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ADRENOCORTICOTROPIC HORMONE (ACTH)

Its Effect in Bronchial Asthma and Ragweed Hay Fever

By
THERON G. RANDOLPH, M.D., F.A.C.A.
and
JOHN P. ROLLINS, M.D.
Chicago, Illinois

RELIEF of chronic bronchial asthma following the administration of adrenocorticotropic hormone (ACTH) was first observed by us in June, 1949; this occurred in a case of advanced rheumatoid arthritis[3] complicated by bronchial asthma. The ability of ACTH to bring about improvement in chronic allergic symptoms was not surprising in view of its specific action in rheumatoid arthritis.[2] Zeller[18] recently reported clear-cut evidence that rheumatoid arthritis responds favorably to the elimination of specific food allergens and reviewed earlier contributions in respect to the allergic concept of this disease. Our clinical experience not only confirms the specific etiology of food allergens in arthritis, but we have also observed improvement in such cases following the specific diagnosis and treatment of inhalant allergy.[6,9]

These preliminary observations led us to study the effects of ACTH in bronchial asthma and other allergic syndromes. Pilot observations were made on three patients with chronic asthma, preliminary observations of which have previously been reported.[13] The clinical response of these three patients, whose histories are herewith reported in detail, prompted an evaluation of ACTH in the treatment of other allergic syndromes.

Patients with severe perennial bronchial asthma, refractory to conventional allergic management including prolonged periods of hospitalization, were selected for this study. They were hospitalized and the following determinations were made during a period of forty-eight hours prior to,

Dr. Randolph is an instructor in internal medicine and Dr. Rollins is a research fellow in internal medicine, Northwestern University Medical School.
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during the interval of administration of ACTH, and for several days thereafter: (1) The average of three maximum expirations was taken as the vital capacity, charted in the forthcoming figures by the upper solid line. (2) The time required to exhale an arbitrarily selected volume of air, the amount being chosen in relation to the patient's vital capacity and measured in terms of the cubic centimeters of air expired per second, was designated the expiratory rate. This technique, modified after that originally described by Hamburger,[1] will be described in detail elsewhere.[17] The expiratory rate is plotted in the figures as the second (broken) line. (3) The absolute number of circulating eosinophils per cu. mm. of blood was determined by employing the direct counting chamber glycol stain technique previously described[5]; it is shown graphically by the lower solid line. (4) Individual food tests[8,14] with known food allergens were performed within a three week period prior to hospitalization and repeated either during the course of or immediately following the administration of ACTH. (5) All epinephrine was discontinued for twenty-four hours immediately prior to the administration of ACTH, and aminophylline was administered as necessary for the relief of severe asthma.

Inspiratory and expiratory chest x-ray films were made prior and after the full therapeutic effect of ACTH had been obtained.

Case 1.—C. P., unemployed male, aged forty-three, developed acute sinusitis in December, 1942, which continued throughout the winter. In March, 1943, he developed his initial attack of bronchial asthma which continued for a month until the onset of lobar pneumonia. During the period of and for a month following his pneumococcus infection he remained free of asthmatic symptoms. Severe bronchial asthma then recurred and has been present perennially to an incapacitating degree since this time except for temporary relief obtained during prolonged fasting. In 1945 all food was avoided for a twenty-one day period; after the eleventh day he remained completely free of asthma and rhinitis, was able to walk between two and five miles daily and lost a total of 21 pounds in weight. Three days after returning foods to his diet he had recurrence of his formerly severe rhinitis and asthma.

He has received many types of treatment, including repeated polypectomies, bilateral Caldwell-Luc operation, radium therapy of the sinuses, x-radiation of the lungs, and repeated attempts to diagnose and treat inhalant and food allergy.

Although we have been able to show by experimental individual food tests[8,14] that the ingestion of each of several major allergenic foods would cause a sharp accentuation in his asthma and their complete avoidance would bring about some improvement, he has never obtained sufficient relief of asthma to be able to earn a livelihood. Although known to be dust sensitive clinically, each attempt to diagnose or treat his house dust allergy has resulted in an accentuation of symptoms, regardless of the exceedingly low levels at which therapy was instituted.

One week prior to hospitalization in August, 1949, an individual food test with orange was followed by a marked accentuation of his chronic asthma.

Figure 1 shows the serial observations of his ventilatory capacity and eosinophil levels prior to, during and following the administration of 225.0 mg. ACTH, given in 25.0 mg. doses every six hours. One should note the initial increase in eosinophils prior to starting treatment which occurred with the cessation of epinephrine administration. In order to keep these initial observations constant, he was maintained on his formerly restricted diet prior to and following therapy with ACTH. His sense

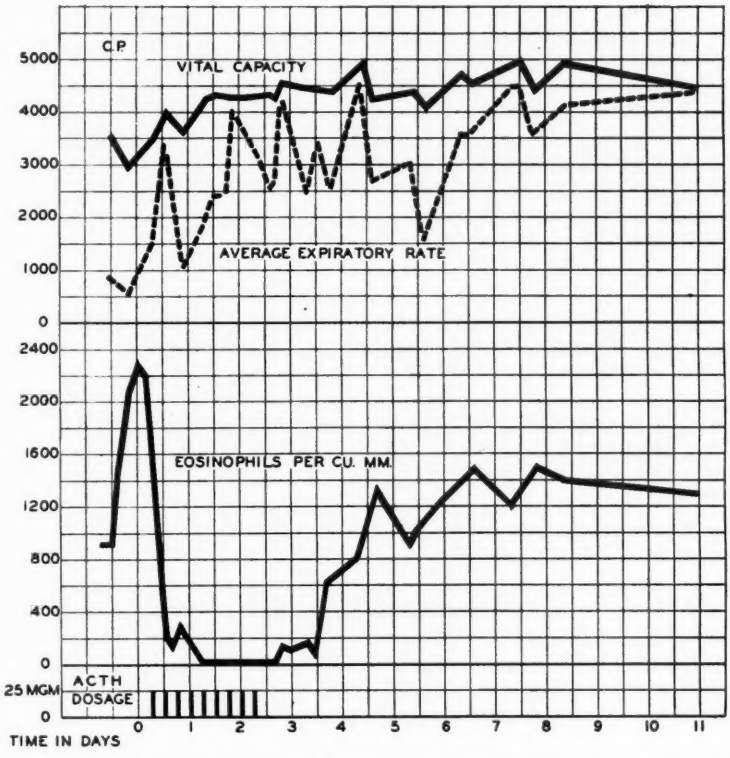

Fig. 1. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in C.P., a patient with bronchial asthma, following ACTH therapy.

of smell recurred, his nose became patent and he had complete relief of his rhinitis and asthma within twenty-four hours after starting therapy with this hormone. Although relative anosmia recurred after four days, he remained without troublesome allergic symptoms and required no symptomatic measures for their relief during a total period of three weeks. At the beginning of the fourth week from the time of starting therapy his asthma recurred, and in spite of the use of symptomatic measures it reached its former degree of severity within a week.

The experimental ingestion of orange failed to produce allergic symptoms when fed during the course of therapy and again when fed four days after the cessation of ACTH. There was no change in his skin test response to house dust as measured by serial dilution testing[6,15] after ACTH therapy as compared with identical tests before treatment. Whereas intradermal skin testing with house dust extract (Endo) prior to the administration of ACTH had been followed by a constitutional reaction on each of three different occasions, repetition of the procedure failed to produce symptoms immediately after treatment with ACTH.

A month after the first course of ACTH he was again hospitalized at which time he was having asthma of the former degree of severity. He was given an identical course of ACTH and responded in a similar manner even though returned to a general, unrestricted diet immediately after the cessation of therapy. He remained

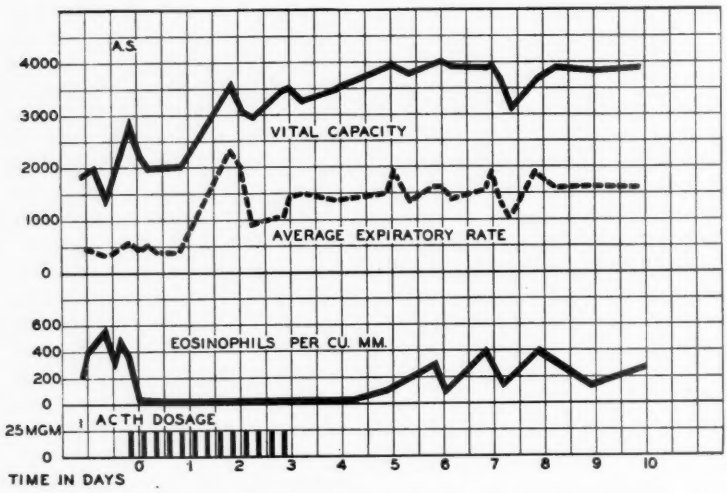

Fig. 2. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in A.S., a patient with bronchial asthma, following ACTH therapy.

free of asthma and other allergic symptoms for a period of two and one half weeks.

This course of events has been repeated two additional times. During the third course he obtained less effective relief and on his own initiative returned to his former restricted diet. Under these circumstances he remained free of troublesome asthma for a period of three weeks although the occasional use of epinephrine by inhalation was necessary for relief of mild symptoms.

During the fourth course of ACTH in the same dosage he chose to follow his restricted diet and was more satisfactorily relieved of allergic symptoms than during the third course of therapy.

Case 2.—A. S., retired farmer, aged seventy-five, had been subject to perennial bronchial asthma since the age of sixty-two years. His most troublesome symptoms occurred between four and six in the afternoon and during the night, although he had some asthma continually, in spite of large doses of aminophylline, epinephrine, and oxygen by inhalation several times daily. He had been subject to hay fever during the mid and late summer for several years. He had also been found clinically sensitive to aspirin, ephedrine and Orthoxine.

His asthma had formerly been accentuated on exposure to barn dusts but this contact had not been present since his retirement at the age of sixty-three. Other precipitating agents were not suspected.

He was studied allergically in 1940 and again in 1949. On both occasions he was found skin-test sensitive to ragweed and gave slightly positive intracutaneous reactions to house dust. However, specific therapy with house dust and ragweed extracts did not significantly change his chronic symptoms. He was found highly sensitive to wheat and rye as a result of experimental feeding tests in 1940, but the avoidance of these foods was only partially effective in controlling his asthma. When restudied in 1949, all the major allergenic foods were appraised by means of individual food tests;[8,14] he was found highly sensitive to corn, wheat, rye and pork as evidenced by the production of sharp attacks of asthma following these ingestion tests.

This patient was hospitalized in late August during the height of the ragweed

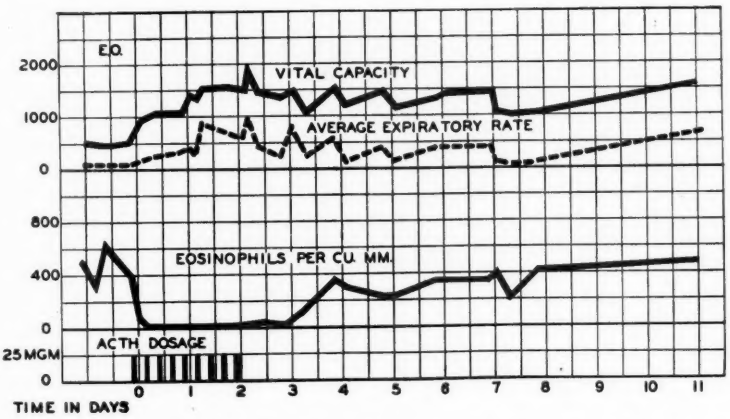

Fig. 3. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in E.O., a patient with bronchial asthma, following ACTH therapy.

pollinating season, and was treated with 325 mg. of ACTH in divided doses over a period of three days. Sustained improvement in his asthma was noted during the second day of therapy, and symptomatic medications were no longer necessary at the end of the third day. Changes in his ventilatory capacity and eosinophil response are shown in Figure 2. At this time his known allergenic foods were returned to his diet one by one and failed to produce respiratory or other allergic symptoms. He returned home on a general diet, resumed a normal degree of activity for his age and required no symptomatic medications for a period of three weeks.

Upon the recurrence of severe asthma during the fourth week, he was rehospitalized and treated with 225.0 mg. ACTH. Although the pattern of his response was similar to that following his initial course and his improvement persisted for approximately the same duration, there was a detectible clinical difference in the degree of relief in that he had occasional attacks of mild symptoms from which he obtained immediate relief with small doses of epinephrine by inhalation.

Six weeks after this course of therapy and in a state of relapse, he was rehospitalized and treated with Concentrated Adrenal Cortex Extract,[10] and although improved while therapy was maintained, severe asthma recurred three days after stopping treatment.

One week later he received a course of Cortisone therapy; this will be described subsequently.[11] Seven days after the cessation of Cortisone and sixteen days following cessation of therapy with cortical extract, he was given a third course of 225.0 mg. ACTH. This was followed by a clinical response comparable in degree and duration to that of the second course of ACTH. It should be emphasized that he has remained on a general diet eating his known food allergens without restrictions since the completion of the initial course of ACTH therapy.

Case 3.—E. O., a woman, aged fifty-five, subject to chronic perennial bronchial asthma and allergic rhinitis since the age of forty-five years, was chosen for this study because of incapacitating asthma which was complicated by a marked degree of pulmonary emphysema. Her continual dyspnea was of such a degree that for several years she had been unable to talk in complete sentences or to walk up a single flight of stairs.

Allergic study in the summer of 1949 revealed an equivocal intradermal reaction

to house dust, but specific therapy, according to the technique outlined,[6] failed to change the course of her disabling symptoms. On the performance of individual food tests she developed attacks of acute bronchial asthma following the trial ingestion of rye, potatoes, milk and string beans. However, the specific avoidance of incriminated foods was only partially effective in relieving her symptoms.

Improvement in her asthma and dyspnea was first noted six hours after the initial injection of 25.0 mg. ACTH. After twenty-four hours of therapy this patient was able to talk in full sentences, to walk briskly in the hospital corridors and up a flight of stairs without dyspnea. The repetition of food tests which were formerly associated with the development of acute rhinitis and asthma now failed to produce allergic symptoms. However, aside from these trial tests, she was continued on her restricted diet during and following the initial course of treatment. She remained free of asthma and rhinitis without the need of medications and led a normal life for the following two and one-half weeks. Ventilatory and blood observations are shown in Figure 3.

Thereafter, she showed a gradual recurrence of asthma, and when this reached the former degree of severity she was rehospitalized for a second identical course of ACTH. Although her immediate response was identical to that of the first course, a pronounced weakness developed two days after the cessation of therapy. She was then returned to a general diet with the exception of milk and within a few days her weakness subsided. In other respects her clinical response to this course of ACTH therapy was similar to that of the initial one.

By the time the first course of treatment in the three above cases was completed it became evident that a more extensive study of the effects of ACTH in allergic diseases was indicated. Eight additional asthmatics were studied similarly.

Case 4.—S. H., a man, aged fifty-five years, with a history of intermittent bronchial asthma since the age of ten years, had continuous severe rhinitis and asthma for the past decade. His asthma was complicated by recurrent nasal polypi, aspirin sensitivity and pulmonary emphysema. He received 225 mg. ACTH over a period of forty-eight hours and showed a 75 per cent improvement in his rhinitis and a 50 per cent improvement in his asthma which persisted for only one week. He began using epinephrine by inhalation five days after the cessation of therapy.

Case 5.—B. D., a woman, aged forty-five, with asthma of ten years' duration and known to be clinically sensitive to aspirin, house dust and several major foods had been confined to her bed with incapacitating asthma for the past year prior to starting ACTH therapy. X-ray examination of the chest showed moderate emphysema, residues from previous pleurisy, and obliteration of the right costo-phrenic angle resulting from an old empyema. Her vital capacity doubled following therapy with 225.0 mg. ACTH. This was followed by a clinical response comparable in degree and lief of asthma for a period of two and one-half weeks.

Case 6.—M. H., a woman, aged fifty-six, subject to severe bronchial asthma for twenty years, had been taking 30 grains of aminophylline and eight to ten subcutaneous injections of epinephrine and repeated inhalation of Isuprel daily prior to starting ACTH therapy. She had fractured ribs on several occasions during severe attacks. Her asthma was complicated by moderate pulmonary emphysema and suggestive evidence of pulmonary fibrosis. Her vital capacity also doubled after receiving 225 mg. ACTH. She experienced a marked improvement in her asthma and as-

sociated allergic rhinitis for the following three weeks, during which time aminophylline was not necessary and she was able to reduce materially the use of epinephrine.

Six additional patients with severe bronchial asthma but without pulmonary complications were also treated with Adrenocorticotropic hormone.

Two patients with seasonal ragweed asthma were relieved of all allergic symptoms for the remainder of the 1949 ragweed pollinating season; their cases will be summarized subsequently.

Case 7.—One male child, R. K., aged ten years, with a history of perennial bronchial asthma of four years' duration and known to be clinically sensitive to house dust, ragweed pollen, fungi and several major foods, received a total dose of 140.0 mg. ACTH over a period of three days. This patient had immediate relief of asthma but had a moderate recurrence of wheezing for two days after returning to his home. He then remained entirely free of asthma for the following month, although in previous years this particular season had been his most troublesome period.

Case 8.—W. E., a man, aged sixty years, subject to perennial allergic rhinitis for ten years and bronchial asthma for one year, had complete relief of allergic symptoms for three weeks after receiving 300 mg. ACTH over a period of three days.

Case 9.—E. U., a man, aged fifty-two, developed perennial nasal allergy at the age of forty-seven which was subsequently complicated by nasal polypi. Within a few hours after his initial polypectomy at the age of forty-eight, he developed severe bronchial asthma which has been present constantly since except for a period of two and one-half months immediately following insulin shock therapy received as treatment for an acute toxic psychosis. An initial course of only 125 mg. ACTH was given because of progressive edema and gain in weight beginning after the fourth dose of 25.0 mg. Although he developed the expected degree of eosinopenia, there was no significant change in the severity of his asthma except for transient improvement during ACTH administration.

A second course of the same amount given three weeks later was followed by moderate improvement during the period of administration which persisted only for a four-day period. A comparable gain in weight and clinical edema again developed which prompted us to discontinue therapy.

A third course two weeks later, consisting of 50 mg. daily in divided doses for three days, failed to produce edema or to cause any improvement in his asthma. Subsequently, this patient was diagnosed specifically and found sensitive to milk. The removal of milk and wheat from his diet has been more effective in controlling his asthma than ACTH administration in the dosage schedules employed. Although the cumulative addition of wheat was tolerated, each attempt to reintroduce milk has resulted in acute abdominal cramps and diarrhea.

Case 10.—J. S., aged fifty-eight, and previously reported by Markson,[3] had been subject to rheumatoid arthritis for twelve years and mild perennial bronchial asthma for one year prior to starting ACTH therapy June 20, 1949. He has received a daily dosage of ACTH sufficient to control his rheumatoid arthritis since. While he was treated for his arthritis, we noted a gradual improvement in his asthma during the first twelve days of therapy; this was based on clinical evidence as well as a change in his expiratory rate from 800 to 1,700 c.c. per second.

Although undiagnosed and untreated from the allergic standpoint, he continued without troublesome asthma since this time, except for periods beginning four months

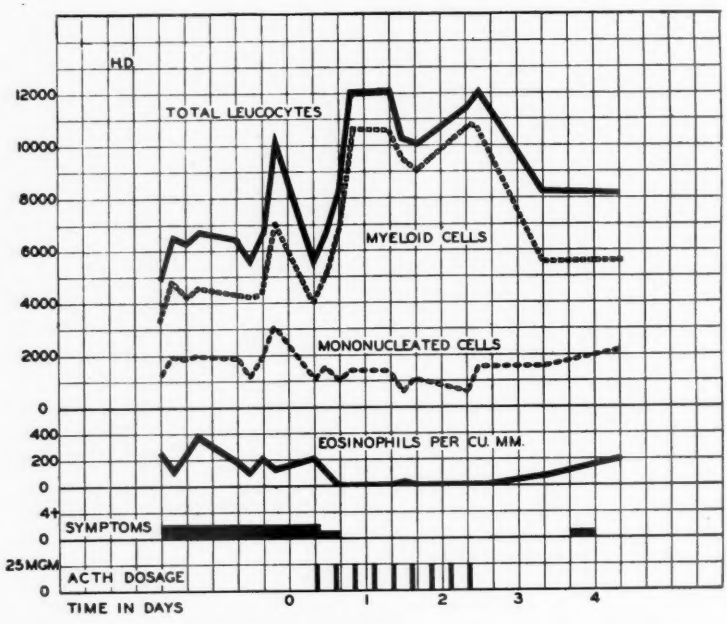

Fig. 4. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in H.D., a patient with ragweed hay fever, following ACTH therapy.

after the institution of therapy when attempts were made to reduce the amount of ACTH to a minimum dose capable of relieving his arthritic pain. During these periods when receiving 12.5 mg. ACTH daily, his asthma recurred in its former severity.

Three patients with acute ragweed hay fever were hospitalized between the dates of August 30 and September 5, 1949; they were placed in corner rooms with open windows. The ragweed pollen count remained over 300 per day throughout the period during which the following observations were made.

The number of times per twenty-four hours that each patient sneezed, sniffled, coughed or blew her nose was recorded for forty-eight hours prior to, during the course of and for four days following the completion of ACTH therapy. Eosinophil, total leukocyte, myeloid and mononucleated cells were determined by the method previously described. Pre- and post-treatment skin tests, skin biopsies and passive transfer studies were made; these will be reported in a subsequent article.

Case 11.—H. D., a woman, aged fifty, had been subject to yearly hay fever from mid-August to the second week of October since 1944. She had received preseasonal specific therapy since the onset of her ragweed symptoms. She also had been subject to typical rheumatoid arthritis of twelve years' duration.

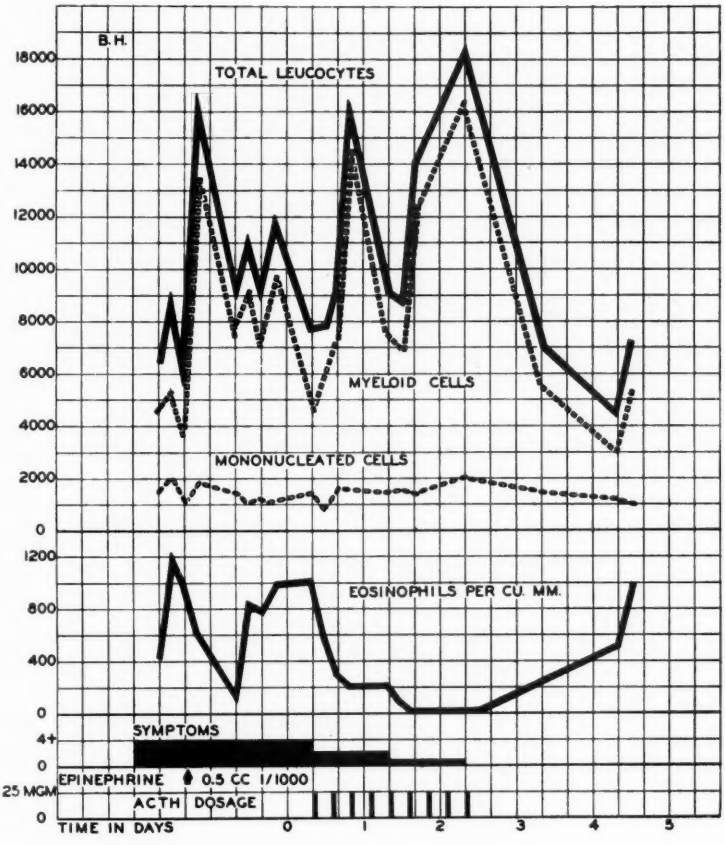

Fig. 5. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in B.H., a patient with ragweed hay fever and bronchial asthma, following ACTH therapy.

She received 225 mg. ACTH in divided doses over a period of forty-eight hours. Evidence of improvement in her nasal symptoms, first noticed thirty minutes following the initial injection of 25.0 mg., progressed to complete relief of hay fever at the end of six hours. Aside from mild sneezing in the afternoon of the third day, she had no further hay fever throughout the remainder of the ragweed hay fever season. Her arthritic symptoms also improved but recurred ten days after the cessation of ACTH therapy. Variations of the blood elements and a summary of the clinical data are shown in Figure 4.

Case 12.—B. H., a woman, aged thirty-eight, had been subject to perennial nasal allergy with superimposed severe ragweed hay fever for the past sixteen years, complicated by seasonal bronchial asthma for the past twelve years. As may be noted in Figure 5, she developed leukocytosis and eosinopenia immediately after an

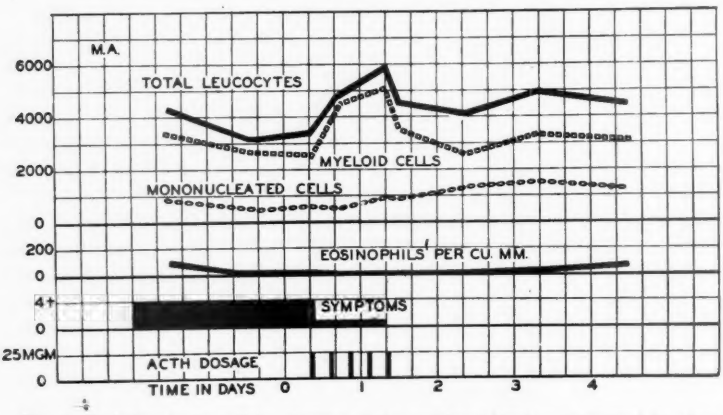

Fig. 6. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in M.A., a patient with allergic headache, ragweed hay fever and bronchial asthma, following ACTH therapy.

injection of 0.5 c.c. epinephrine which had been given in order to control severe asthma developing immediately following skin testing with ragweed extract.

She received 225 mg. of ACTH during a period of forty-eight hours. Her respiratory symptoms began to improve thirty minutes after the first dose of 25.0 mg. and were completely relieved at the end of forty-eight hours. Repetition of the skin tests at this time failed to produce any symptoms. She had no further hay fever or asthma for the remainder of the pollen season, and her perennial rhinitis remained 50 per cent improved for the following four months compared with the severity of her symptoms during a comparable period in previous years.

Case 13.—M. A., physician's wife, aged thirty-seven, had been subject to perennial rhinitis and severe incapacitating headaches since childhood. These symptoms had been relieved for a period of two years as a result of dust therapy and the avoidance of several major allergenic foods. An intractable cough which began in April, 1949, was controlled by the additional avoidance of beet and cane sugar. In each instance, individual food tests with cane sugar and with beet sugar were followed in ten minutes by the onset of violent coughing. Similarly, the accidental or inadvertent ingestion of either type of sugar had been followed by the precipitation of coughing.

Her initial ragweed hay fever and bronchial asthma developed while on a motor trip at the height of the 1949 pollen season, necessitating her return to the hospital September 5, 1949. During the twenty-four-hour period prior to ACTH therapy she sneezed, sniffled, coughed or blew her nose 640 times. She was maintained on her formerly restricted diet during the course of administration of 125 mg. ACTH. A decrease in the incidence and severity of sneezing occurred forty minutes after the initial intramuscular injection of 25.0 mg.

Fifteen minutes after each injection of 25.0 mg. ACTH this patient experienced a transient vasoconstriction with pallor and coldness of her extremities but without a significant change in her blood pressure. These manifestations were attributed to the small quantity of posterior pituitary fraction present in this material. Three hours after the initial injection she complained of bilateral deep pelvic pain which radiated caudally and anteriorly into the groin. She remarked that this pain was identical in character to premenstrual pain present prior to surgical removal of the left ovary and x-ray castration of the right ovary four and three years previously,

respectively. As additional treatment was given every six hours, these continued with sufficient intensity to require the use of opiates for relief. Since we felt that an adequate therapeutic response had been obtained and that these symptoms might represent an overdosage phenomenon, her ACTH therapy was discontinued after five intramuscular injections totalling 125.0 mg. These pelvic symptoms persisted for a week after the cessation of treatment.

Forty-eight hours after the completion of ACTH therapy, her beet and cane individual food tests were repeated but failed to produce symptoms. She was then returned to a general unrestricted diet. With the exception of estrogen therapy which was begun following castration, discontinued during ACTH therapy and restarted 5 days after stopping ACTH, she received no other type of medication.

Following massive dust exposure in January, 1950, at the height of the house dust season,[16] she developed a recurrence of coughing, asthma, headache and generalized edema with a gain in weight of 15 pounds. These symptoms were promptly relieved following a second course of 225 mg. ACTH. This patient showed a progressive weight loss coincident with a marked diuresis during the first five days after the onset of ACTH therapy. During the second day of therapy she had a recurrence of her formerly described pelvic pain for the first time since her previous course of ACTH. Although she has again had complete relief of her allergic symptoms, this pain has persisted up to the present time, that is, two weeks after treatment with ACTH.

DISCUSSION

With the exception of the two cases of seasonal ragweed asthma, the other asthmatics selected for this study of the effectiveness of adrenocorticotropic hormone in bronchial asthma were perennial advanced cases of this disease. As judged from the age of the onset of asthma, the majority of these patients would qualify for the designation of "intrinsic asthma" as described by Rackemann.[4] Furthermore, several of the cases were complicated by nasal polypi and aspirin sensitivity, a combination which has been striking in respect to the difficulty in the management of bronchial asthma from the standpoint of specific allergic diagnosis and therapy. It should be re-emphasized that the patients chosen for the administration of ACTH were not a random sample of bronchial asthma but represented the most difficult diagnostic and therapeutic problems gleaned from a private practice of allergy.

Ten of the eleven asthmatics to whom a short course of ACTH had been administered obtained a marked degree of relief of their chronic symptoms. The duration of relief varied from a week to as long as five months following a single course of therapy, ranging in total dosage of ACTH from 125.0 to 325.0 mg. One case, E. U., developed evidence of fluid retention early in the course of each of two attempts to treat him with ACTH in a manner found effective in the other asthmatics. Although he failed to develop edema in the third course of ACTH at a lower dosage level, he also failed to show a significant degree of improvement in his allergic symptoms when treated for a period of time found to be effective in other cases.

We have had the opportunity of observing only one patient, J. S.,[3] treated with continuous ACTH therapy. This arthritic patient with mild

complicating bronchial asthma has received a dosage varying from 12.0 to 75.0 mg. daily for the past eight months. As previously stated, his asthma recurred when treated for several days at the lower level of dosage although he remained free of arthritic pain. With a further reduction in dosage his arthritic pain also recurred.

In general, prolonged continuous therapy for the treatment of bronchial asthma does not seem to be indicated in view of the response obtained from short intermittent courses of therapy.

The degree of relief of asthma in the ten cases showing a favorable response varied from complete to approximately 50 per cent. By complete relief is meant an absence of rhonchi as detected on repeated chest examinations, the maintenance of normal vital capacities in respect to the individual's surface area and the ability to lead normal lives without obvious wheezing in the absence of taking medications for the relief of asthmatic symptoms. In general, the most striking results were obtained in those cases uncomplicated by other pulmonary pathology. ACTH was least effective in the asthmatics shown by x-ray and clinical evidence to have pulmonary emphysema, extensive scarring resulting from pleurisy and empyema. Our experience has shown that in most instances the greater the degree of pulmonary emphysema the less satisfactory was the clinical response to ACTH administration. The outstanding exception to this statement is the case of E. O.

Not only is adrenocorticotropic hormone effective in relieving temporarily the symptoms of severe, long sustained bronchial asthma, but it also changes the reactivity of allergic individuals known to be specifically sensitized to food and inhalant allergens. In several instances foods known to produce acute accentuations in bronchial asthma prior to the administration of ACTH were tolerated without evidence of symptoms during the course of and for a period of time following ACTH therapy. Similarly, test procedures with house dust and ragweed pollen which produced constitutional reactions prior to therapy failed to do so during or immediately following treatment with adrenocorticotropic hormone. It should be emphasized, however, that ACTH seems capable of producing only a transient refractoriness to known allergenic offenders.

With the recurrence of bronchial asthma following a course of ACTH therapy, symptoms are readily relieved following the inhalation of a small amount of epinephrine spray. This is in decided contrast to the ability of epinephrine to relieve symptoms of similar severity prior to the administration of ACTH. Whereas an individual might have found it necessary to inhale 1:100 epinephrine eight to ten times prior to hormone therapy to obtain relief from an attack of asthma, literally a "whiff" of the 1:100 concentration effects prompt relief of asthma of comparable severity after ACTH therapy. This change in the effectiveness of epinephrine is only temporary.

ACTH appears to be a remarkably effective agent in bringing about com-

plete relief of ragweed hay fever as evidenced by the striking results in three patients treated during the height of the 1949 ragweed hay fever season. Not only did this therapy eradicate all evidences of clinical hay fever but protected the three individuals so treated for the remainder of the current ragweed pollinating season. The effect on the skin tests and passive transfers of these patients to ragweed pollen extracts will be presented in another publication.[19]

In addition to the relief of asthma and rhinitis as a result of ACTH treatment, these patients usually experienced marked general improvement, in that they noted an increased warmth of their extremities, an apparent increased vascularity of the nail beds and skin; they claimed to feel less tense and apprehensive, more relaxed and tranquil. That improvement in these symptoms as well as the asthma was not due to suggestion is attested by the fact that in many instances the patients were unaware of the exact time at which ACTH therapy started, placebos containing a small amount of propylene glycol in saline having been administered intramuscularly for several doses prior to the administration of ACTH with the patient understanding that he was receiving potent preparations. In no instance did evidence of clinical improvement occur under such circumstances.

Variations in the blood elements following ACTH therapy has been discussed in previous publications.[7,12] In general, these consist of an initial decrease in the total leukocyte count, followed by a leukocytosis and eosinopenia.

We have not observed any deleterious effects from ACTH in allergic individuals treated with short-term intermittent courses of therapy as outlined in this communication. Neither has there been any unpleasant side effects with the exception of the so-called pelvic cramps in the case of M. A. We wonder if these symptoms may have been the result of stretching of the adrenal capsule as a consequence of transient enlargement of the gland, or possibly as the result of hemorrhages in the adrenal cortex.

In our experience in treating allergic individuals with ACTH, we have learned to watch for the following course of sequential events: The dosage of ACTH is started at 25.0 mg. intramuscularly every six hours with the aim of obtaining a prompt and maximum glandular stimulation of short duration. It is continued at this level even though the eosinophils markedly diminish or disappear from the peripheral blood; this usually occurs within twenty-four hours from the time of the first dose. We observe the patient's fluid intake and output as well as the daily weight for, as a rule, the dosage is reduced 50 per cent in the event of a definite oliguria or a gain in weight of 2 to 3 pounds in twenty-four hours. Most adult patients and some children, particularly those with eczema, tolerate ACTH therapy at a dosage of 25.0 mg. every six hours for a total of nine doses without hazard even though there is no deliberate attempt made to regulate the electrolyte balance.

It should be emphasized, finally, that dangers said to be associated with

ACTH therapy pertain to long-continued treatment and thus far in our experience have not been observed in therapy consisting of short intensive courses followed by relatively long rest periods as employed in this study.

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CORRECTION

In the volume Allergy in Relation to Otolaryngology by French K. Hansel, M.D., F.A.C.A., published recently by The American College of Allergists, the question on page 72 was wrongly attributed to Kenneth L. Craft, M.D. The correct name is Bennett Kraft, M.D., F.A.C.A., Indianapolis, Indiana.

ADRENOCORTICOTROPIC HORMONE (ACTH)

Gross and Histologic Effects on Skin Tests and Passive Transfer

MICHAEL ZELLER, M.D., F.A.C.A.,
THERON G. RANDOLPH, M.D., F.A.C.A., and JOHN P. ROLLINS, M.D.
Chicago, Illinois

DURING the course of therapy of various allergic states with adrenocorticotropic hormone, it was considered that a study of skin responses might elucidate to some extent the action of the drug. Patients with hay fever were selected for the study because of the constancy of skin responses as related to clinical symptoms.

Histologic studies of the allergic wheal reported by Berger and Lang,[2,3] and Kline, Cohen and Rudolph[6] reveal that eosinophilia in the inflammatory exudate is the most constant finding. The latter authors state that twenty to thirty minutes after the injection of the allergen there was pronounced inflammation with the majority of the wandering cells consisting of eosinophils.

In the light of these findings our own histologic studies were done twenty to fifty-five minutes after the injection of allergen. Serial biopsies were not possible, for the study was limited to two patients because of scarcity of the drug.

PROCEDURE

Two patients, H. D. and B. H., with ragweed hay fever were admitted to the hospital August 30, 1949. Scratch tests with thirty-six common pollens and animal danders were done and recorded. Intradermal serial dilutions of ragweed were applied to the arm and the reactions noted. Two hours later .02 c.c. of 1:500 ragweed solution was injected intradermally in the left lower abdominal quadrant. Twenty-five minutes after injection of the ragweed a diamond-shaped area 5 cm. from the wheal was infiltrated with two per cent procaine. A biopsy of the skin including the wheal and surrounding erythema was then taken. One of the patients, B. H., developed a generalized reaction with asthma and urticaria necessitating four minims subcutaneous epinephrine prior to completion of the biopsy.

Passive transfer was done by injecting intradermally .15 c.c. blood serum of subject H.D. into the right and left lower abdominal quadrants of ragweed non-sensitive recipient P and into left lower abdominal quadrant of recipient R. The serum of subject B.H. was similarly injected into ragweed non-sensitive recipient Z. Twenty-four hours later a skin biopsy of the sensitized site, using the technique already described, was taken from recipient P without ragweed injection. Recipients R and Z were injected

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

The adrenocorticotropic hormone (ACTH) was supplied by Armour and Company through the courtesy of Dr. John R. Mote.

The histologic studies were made by Dr. H. Ivan Brown, pathologist of the Ravenswood Hospital, Chicago, Ill.

with .02 c.c. of the 1:500 ragweed extract at the sensitized sites, following which a wheal with pseudopods 2 cm. in diameter developed in recipient R and 4 by 5 cm. in recipient Z. Skin biopsies including the wheals with surrounding erythema were taken thirty minutes after ragweed injection in recipient R and fifty minutes after ragweed injection in recipient Z. Control ragweed injections produced circular whealing measuring 4 mm. with surrounding erythema of 2 mm. Forty-eight hours after passive transfer a second skin biopsy was taken from recipient P thirty-five minutes after injection of .02 c.c. of 1:500 ragweed extract into the remaining sensitized area in the right lower abdominal quadrant.

Treatment of the two hay fever patients with adrenocorticotropic hormone (ACTH) was started at 9:00 a.m., September 2, 1949, and stopped at 9:00 a.m., September 4, 1949, when the number of eosinophils per cu. mm. of blood were zero in subject H.D. and 56 in subject B.H. At 9:30 a.m. scratch tests and serial intradermal ragweed extract were applied to both hay fever subjects and recorded as prior to adrenocorticotropic hormone therapy. At 11:00 a.m. of September 4, 1949, .02 c.c. of 1:500 ragweed extract was injected intradermally into the right lower abdominal quadrant of hay fever subjects H.D. and B.H. Thirty and fifty-five minutes later, after whealing, skin biopsy was performed as before. At 4 p.m. September 4, 1949, .15 c.c. of post-ACTH treatment serum of subject H.D. was injected intradermally into the right lower abdominal quadrant of recipient R. The post-ACTH treatment serum of subject B.H. was similarly injected into recipient Z.

Forty-eight hours after passive transfer with post-ACTH treatment serum, .02 c.c. of 1:500 ragweed extract was injected intradermally into the sensitized areas of recipients R and Z. Skin biopsies were again taken as described with pre-ACTH treatment serum. Control ragweed injections into non-sensitized areas produced reactions similar to the previous controls.

The skin specimens were then prepared in the routine manner and stained with hematoxylin and eosin.

Three ragweed sensitive patients, H.D., B.H., and M.N., were skin tested in the left side of the back with scratch and intradermal ragweed extract, histamine and ACTH. The ACTH in this study consisted of 25 mg. dissolved in 2 c.c. of normal saline solution. The histamine solution contained 1 mg. of histamine phosphate per c.c. (a 1:1000 solution), equivalent to 0.36 mg. of histamine base. The intradermal ragweed solution consisted of 1:500 dilution, and for the scratch test the concentrated ragweed extract was used. Thirty minutes later mixtures of ⅔ ACTH solution and ⅓ each of ragweed and histamine were applied on the right side of the back by the scratch and intradermal methods as in the controls. Two hours later ragweed hay fever subjects H.D., B.H. and M.N. were scratch tested with ragweed extract on the right forearm at three sites 3 cm. apart, and the usual whealing and erythema was noted. Twenty minutes later ACTH was

TABLE I. THE WHEALING RESPONSE OF RAGWEED AND HISTAMINE WITH ADRENOCORTICOTROPIC HORMONE ACTH, IN 3 HAY FEVER PATIENTS

Subjects	Materials	Scratch Tests	Intradermal Tests
H.D.	Mixture of:		
B.H. and M.N.	Ragweed, one third ACTH, two thirds	Wheal and Erythema	Wheal and Erythema
	Ragweed control	Wheal and Erythema	Wheal and Erythema
	ACTH control	No reaction	Small circular wheal with erythema
	Mixture of:		
	Histamine, one third ACTH, two thirds	Wheal and Erythema	Wheal and Erythema
	Histamine control	Wheal and Erythema	Wheal and Erythema

TABLE II. THE WHEALING RESPONSE OF RAGWEED SCRATCH TESTS IN SITES PRETREATED 10 MINUTES EARLIER WITH ADRENOCORTICOTROPIC HORMONE, ACTH

Subjects	Materials	Scratch Tests
H.D. B.H. and M.N.	ACTH applied to scratch site. Concentrated ragweed extract applied 10 minutes later	Wheal and erythema
	ACTH control applied to scratch site.	No reaction
	Concentrated ragweed extract control applied to scratch site	Wheal and erythema

first applied to scratch tests on the left forearm, ten minutes after which ragweed was applied at the same site.

RESULTS

Skin Tests.—The thirty-six inhalant extracts applied to the back of the hay fever subjects H.D. and B.H. revealed numerous reactions varying from zero to four plus. The ragweed reactions exemplified the latter degree of reaction. Serial ragweed dilutions from 1:500 to 1:62,500 applied intradermally on the arm likewise revealed whealing and erythema starting from four plus and diminishing in proportion to strength of solution. After treatment with adrenocorticotropic hormone repeat test studies were essentially the same.

The results of the studies shown in Table I clearly indicate that ⅔ adrenocorticotropic hormone mixed with ⅓ ragweed and histamine and applied by scratch and intradermal methods failed to alter the response obtained by ragweed and histamine alone.

In Table II it is shown that the application of adrenocorticotropic hormone to scratch tests followed ten minutes later by ragweed concentrate produces whealing the same as ragweed controls.

Histopathologic Studies.—Tables III and IV. The biopsies taken from the hay fever subjects prior to ACTH therapy reveal eosinophilic infiltration and edema as constant and prominent features. After ACTH therapy the biopsies show absence of eosinophils in one subject and sharp reduction of eosinophils in the other. There is in addition marked increase of polymorphonuclear cells with a decrease of monocytes and lymphocytes.

The sections taken from the passive transfer sites also disclose edema and eosinophilic infiltration, but there is no significant change in the pro-

TABLE III. HISTOLOGIC STUDIES OF SKIN TESTS AND PASSIVE TRANSFERS WITH ADRENOCORTICOTROPIC HORMONE ACTH, IN RAGWEED HAY FEVER, SEPTEMBER, 1949

PRIOR TO TREATMENT WITH ACTH

Subject	Eosinophils Per Cu. MM. of Blood	Subcutaneous Tissue	Corium	Conclusions
Hay Fever H.D.	220 or 3.3 per cent	No tissue in section	Moderate perivascular reaction and edema. Differential in per cent Eos. 25 Polys. 50 Monos. & Lymphs. 25	Allergic Reaction
Hay Fever B.H.	781 or 8.8 per cent	Few vessels. Inflammatory reaction minimal with 10 to 15 cells about each capillary. Differential in per cent Eos. 15 Polys. 75 Monos. & Lymphs. 10	Marked acute inflammatory reaction and edema about all vessels. Differential in per cent Eos. 10 Polys. 70 Monos. & Lymphs. 20	Moderate Allergic Reaction
Passive Transfer Recipient R.	111 or 1.2 per cent	Diffuse inflammatory reaction and edema, particularly about all small capillaries. Differential in per cent Eos. 45 Polys. 35 Monos. & Lymphs. 20	Perivascular inflammatory reaction and edema prominent. Differential in per cent Eos. 5 Polys. 35 Monos. & Lymphs. 60	Severe Allergic Reaction
Passive Transfer Recipient Z.	143 or 1.5 per cent	Slight inflammatory reaction about small capillaries. Moderate edema. Differential in per cent Eos. 15 Polys. 55 Monos. & Lymphs. 30	Moderate inflammatory reaction particularly about small capillaries. Edema prominent. Differential in per cent Eos. 2 Polys. 35 Monos.& Lymphs. 63	Moderate Allergic Reaction

portion or type of cellular infiltration as a result of adrenocorticotropic hormone therapy.

In one recipient biopsy of the serum alone without antigen revealed moderate reaction in the corium with 80 per cent lymphocytes and monocytes and 20 per cent polymorphonuclear cells (Table V). The subcutaneous tissue was normal and the reaction was considered as nonspecific. The sections after ragweed injection revealed the type of reaction observed in the other passive transfer recipients but to a lesser degree.

DISCUSSION AND SUMMARY

It seems clear that scratch and intradermal tests on ragweed sensitive patients are not altered after adequate ACTH therapy for clinical relief. It is evident also that gross and histologic studies of passive transfer sites likewise are not influenced by ACTH therapy. Histologic studies of passive transfer sites produced with pre- and post-ACTH treatment serum reveal characteristic edema and eosinophilic infiltration. There is, however, a sharp contrast in the treated hay fever subject who presents a striking diminution of eosinophils in ragweed wheals in parallel with the blood. Using the technique of one of us[7] quantitative blood eosinophil determination per cubic millimeter prior to ACTH therapy varied from 1265 to 781 in one subject and from 396 to 88 in the other. After treatment

TABLE IV. HISTOLOGIC STUDIES OF SKIN TESTS AND PASSIVE TRANSFERS WITH ADRENOCORTICOTROPIC HORMONE ACTH, IN RAGWEED HAY FEVER, SEPTEMBER, 1949

AFTER TREATMENT WITH ACTH

Subjects	Eosinophils per cu. mm. of blood	Subcutaneous Tissue	Corium	Conclusions
Hay Fever H.D.	0	Moderate inflammatory reaction limited to capillary walls. Differential in per cent Eos. 0 Polys. 95 Monos. & Lymphs. 5	Marked acute inflammation and edema. Vessel walls studded with polys. Differential in per cent Eos. 1 Polys. 89 Monos. & Lymphs. 10	Nonspecific Inflammatory Reaction.
Hay Fever B.H.	55 or 0.21 Per cent	Slight perivascular infiltration. Moderate edema. Differential in per cent Eos. 0 Polys. 90 Monos. & Lymphs. 10	Moderate perivascular inflammation and edema. Differential in per cent Eos. 5 Polys. 65 Monos. & Lymphs. 30	Slight Allergic Reaction in Corium only.
Passive Transfer Recipient R.	Not Done	Diffuse inflammatory reaction and edema, particularly about all small capillaries. Differential in per cent Eos. 35 Polys. 40 Monos. & Lymphs. 25	Marked perivascular inflammatory reaction and edema. Differential in per cent Eos. 5 Polys. 25 Monos. & Lymphs. 70	Severe Allergic Reaction.
Passive Transfer Recipient Z.		Slight inflammatory reaction about small capillaries. Moderate edema. Differential in per cent Eos. 15 Polys. 60 Monos. & Lymphs. 25	Moderate inflammatory reaction, particularly about small capillaries. Edema prominent. Differential in per cent Eos. 2 Polys. 68 Monos. & Lymphs. 30	Moderate Allergic Reaction.

TABLE V. CONTROL HISTOLOGIC STUDIES OF PASSIVE TRANSFER IN THE ABSENCE OF ADRENOCORTICOTROPIC HORMONE ACTH

Subject	Site Prepared for Passive Transfer But Without Addition of Antigen	Site Prepared for Passive Transfer With Addition of Intradermal Ragweed
Passive Transfer Recipient P.	Subcutaneous tissue normal.	Subcutaneous tissue shows scattered inflammatory cells in small numbers. Differential in per cent Eos. 8 Polys. 50 Monos. & Lymphs. 42
	Corium shows slight edema and perivascular exudation. Differential in per cent Eos. 0 Polys. 20 Monos. & Lymphs. 80	Corium shows moderate edema and increased vascularity and exudate. Differential in per cent Eos. 5 Polys. 8 Monos. & Lymphs. 87

with ACTH, blood eosinophils rapidly diminished to 56 in the first and to zero in the second. Histologic studies of ragweed wheals taken at this time disclosed few or no eosinophils in the first subject and diminution of eosinophils in the second subject in contrast to profuse tissue eosinophilia prior to therapy. In addition the polymorphonuclear cells increase and the lymphocytes decrease. This indicates that adrenocorticotropic hormone in the doses employed materially reduces or inhibits blood and tissue eosinophils in the treated patient. The inhibiting factor is either not transmitted to passive transfer recipients or if so in quantities insufficient to be

TABLE VI. HISTOLOGIC STUDIES OF RAGWEED WHEAL BEFORE AND AFTER ADMINISTRATION OF EPINEPHRINE

Subject	Method	Subcutaneous Tissue	Corium
Hay Fever S.H.	Control intradermal injection of ragweed.	Minimal inflammation. Marked edema.	Marked acute inflammatory reaction and edema about all vessels.
		Differential in per cent	Differential in per cent
		Eos. 15	Eos. 10
		Polys. 75	Polys. 70
		Monos. & Lymphs. 10	Monos. & Lymphs. 20
	Ragweed wheal on abdomen, excised 20 min. after injection of epinephrine in arm.		Moderate perivascular round cell infiltration.
			Differential in per cent
			Eos. 0
			Polys. 10
			Monos. & Lymphs. 90

detected by this technique. In one hay fever subject a biopsy of a ragweed wheal taken before ACTH therapy also revealed complete absence of eosinophils following the hypodermic injection of five and two minims of epinephrine given at fifteen-minute intervals respectively. (Table VI.)

Numerous observers[1,4,5,8,9] have demonstrated that histamine antagonists such as Pyribenzamine and Benedryl inhibit allergic wheals when administered orally or locally by application before antigen or as an admixture with antigen. Adrenocorticotropic hormone applied locally in like manner fails to demonstrate such inhibiting action on the ragweed or histamine wheal. Yet, at the same time adrenocorticotropic hormone therapy effects rapid and complete relief of clinical ragweed hay fever and asthma. This suggests altering of the hypersensitivity state of the clinical shock organ without influencing gross skin effects. The histamine antagonists on the other hand modify not only the shock organ in relieving hay fever but alter skin responses as well. This indicates dissimilarity in the mode of action of the two types of drugs, the cause of which is as yet unknown.

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CONCENTRATED ADRENAL CORTEX EXTRACT
Its Effect in Bronchial Asthma and Gastrointestinal Allergy

THERON G. RANDOLPH, M.D., F.A.C.A.
and
JOHN P. ROLLINS, M.D.
Chicago, Illinois

THE favorable effects of adrenocorticotropic hormone (ACTH-Armour) and Cortisone (Compound E-Merck) on rheumatoid arthritis[5,6] and the effects of ACTH on other allergic conditions reported at the recent ACTH Conference (October 21-22, 1949),[2,10,12] and subsequently,[1,3] prompted the use of adrenal cortical extract in bronchial asthma and other allergic syndromes. Consequently, Concentrated Adrenal Cortex Extract in Propylene Glycol*, containing 250 glycogen deposition units per c.c., which are equivalent to 25 mg. of Compound S and 50 mg. Compound E, as determined by biological assay, was used in the following study.

Three patients, including two asthmatics (C. P. and A. S.) and one case of gastrointestinal allergy (M.S.) who had previously responded favorably to one or more courses of ACTH and subsequently had been reported,[10] and one case of bronchial asthma (P. A.) who had not previously received endocrine therapy were selected for this study.

Each of the three asthmatics, who had been subject to severe perennial bronchial asthma and were refractory to conventional allergic management including prolonged periods of hospitalization, were hospitalized; and the following determinations were made during a period of forty-eight hours prior to, during the interval of administration of Concentrated Adrenal Cortex Extract, and for several days thereafter: (1) The average of three maximum expirations was taken as the vital capacity, charted by the upper solid line in Figures 1, 2 and 3. (2) The time required to exhale an arbitrarily selected volume of air, the amount being chosen in relation to the patient's vital capacity and measured in terms of the cubic centimeters of air expired per second, was designated the expiratory rate. This technique was modified after that originally described by Hamburger.[4,11] The expiratory rate is plotted in the figures as the second or broken line. (3) The absolute number of circulating eosinophils per cubic millimeter of blood was determined by employing the direct counting chamber glycol stain technique previously described by one of us;[7] it is shown graphically by the lower solid line in Figures 1, 2, 3, and 4. (4) All epinephrine was discontinued for twenty-four hours immediately prior to the administration of Concentrated Adrenal Cortex Extract, and aminophylline was administered as necessary for the relief of severe asthma.

Similar blood studies were made in the single case of gastrointestinal

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allergy. The total leukocyte count was plotted in the upper solid line; the myeloid, mononucleated and eosinophil cells were plotted in the successive lines of Figure 4.

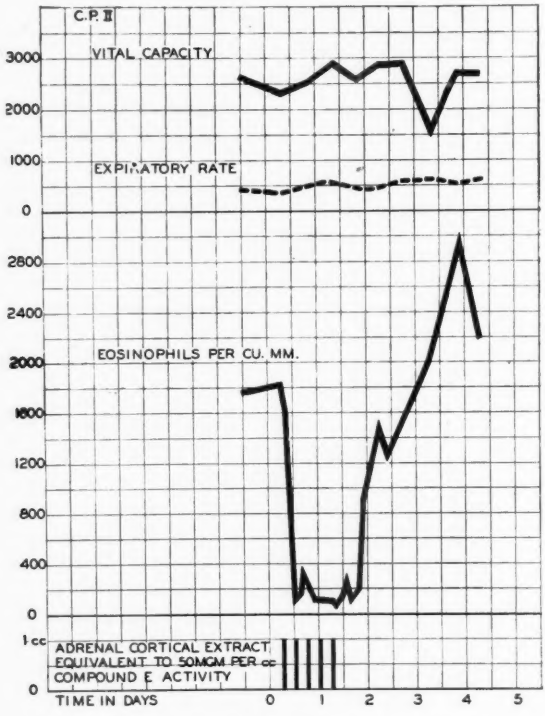

Fig. 1. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in C. P., a patient with bronchial asthma, following treatment with Concentrated Adrenal Cortex Extract.

Case 1.—C. P., a man, aged forty-three years, subject to incapacitating bronchial asthma of seven years' duration, complicated by allergic rhinitis, nasal polypi and chronic sinus infection, was hospitalized in September, 1949, for ACTH therapy. He received 225.0 mg. ACTH in divided doses over a forty-eight-hour period. His pre-treatment vital capacity of 2,850 c.c. of air and his expiratory rate of 500 c.c. of air per second prior to treatment changed to 4,860 c.c. vital capacity and an expiratory rate of 4,500 c.c. per second following this therapy, coincident with relief of his asthma and other allergic symptoms. At the end of the first twenty-four hours of therapy he was not only free of asthma but his sense of smell returned for the first time in many months, and he was able to breath normally through his nose. He remained without troublesome allergic symptoms for the following three weeks, after which he had a gradual return of rhinitis and asthma. He was rehospitalized in October, 1949, with an initial vital capacity of 1,800 c.c. of air and an expiratory rate of 419 c.c. of air per second. After an identical course of ACTH therapy, he again had almost complete relief of allergic symptoms, having a vital capacity of 4,850 c.c. of

air and an expiratory rate of 3,800 c.c. of air per second. This degree of improvement persisted for a two-and-one-half-week period.

Upon the recurrence of asthma of the former degree of severity, he was rehospitalized in October for a course of Concentrated Adrenal Cortex Extract. He received five intramuscular doses of 1.0 c.c. each of this material. Although there was a prompt fall in the level of the peripheral blood eosinophils, there was no significant change either in his vital capacity or expiratory rate as shown in Figure 1. Neither was there a change in the severity of his rhinitis or asthma.

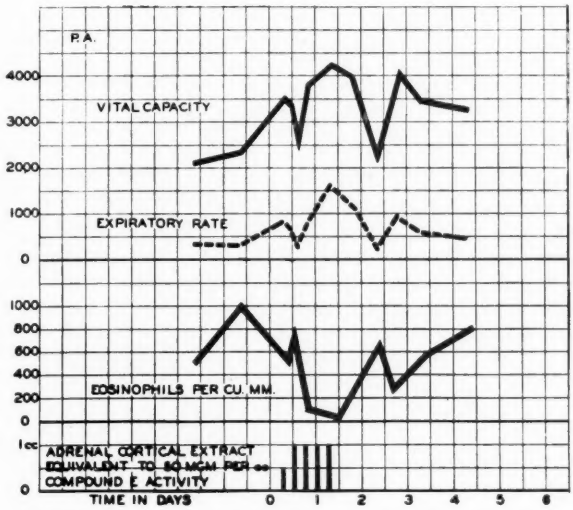

Fig. 2. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in P. A., a patient with bronchial asthma, following treatment with Concentrated Adrenal Cortex Extract.

It has subsequently been shown that he was not refractory to hormone therapy inasmuch as he has since responded on two different occasions to ACTH therapy in a similar manner as he had done prior to treatment with adrenal cortex extract. This response has been described in more detail elsewhere.[8]

Case 2.—P. A., a man, aged fifty-five years, had been subject to incapacitating bronchial asthma for the past seven years and had failed to respond to conventional allergic diagnosis and therapy. For a period of three weeks prior to starting treatment with Concentrated Adrenal Cortex Extract he had been hospitalized for status asthmaticus and treated unsuccessfully by means of the usual symptomatic measures; these included large and frequent doses of epinephrine, aminophylline and various antihistaminics as well as various trial elimination diets. He received an initial dose of 0.5 c.c. and five subsequent doses of 1.0 c.c. of Concentrated Adrenal Extract intramuscularly over a period of two days. There was a transient improvement in his vital capacity and expiratory rate beginning twelve hours after the initial dose of this material, coincident with evidence of improvement as judged clinically, which persisted through the remainder of the period of treatment. His symptoms returned twenty-four hours after the cessation of therapy. This patient also developed a pronounced eosinopenia, as may be noted in Figure 2.

In view of the possibility that the poor clinical response in these two patients may have been due to inadequate therapy with Concentrated Adrenal Cortex Extract, the third asthmatic was treated with a total of

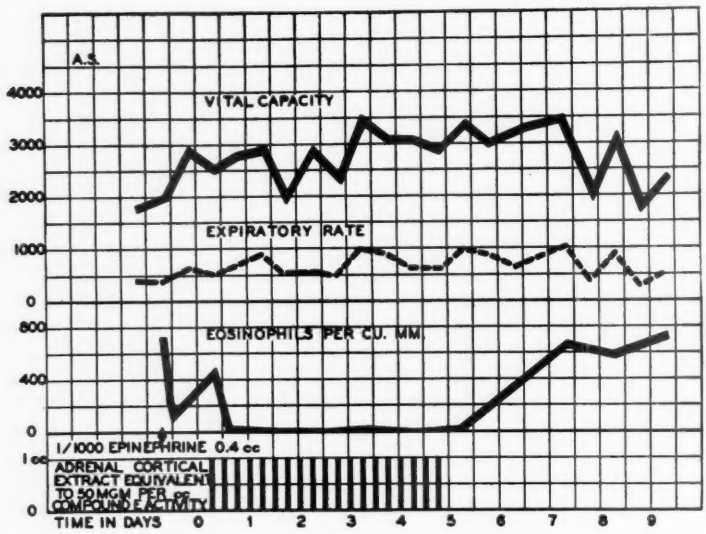

Fig. 3. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in A. S., a patient with bronchial asthma, following prolonged treatment with Concentrated Adrenal Cortex Extract.

19.0 c.c. of this material administered in doses of 1.0 c.c. every six hours over a period of five days.

Case 3.—This patient, A. S., a man, aged seventy-six years, had been subject to bronchial asthma since the age of sixty-two years. For a period of several months prior to his initial therapy with ACTH, he had been receiving oxygen, epinephrine and other symptomatic medications at approximate hourly intervals to control his asthma. He was hospitalized in August, 1949, and received a total of 325.0 mg. of ACTH in divided doses of 25.0 mg. every six hours. By the end of this period of treatment he was able to discontinue all symptomatic medications; his vital capacity had increased from 2,500 to 3,650 c.c., and his expiratory rate had changed from 400 c.c. to 2,500 c.c. of air per second. He was discharged from the hospital and required no symptomatic medications for the following twenty-one days.

In the following week he relapsed to his former level of symptoms, was rehospitalized and given a second course of 225.0 mg. of ACTH, and responded similarly.

Six weeks after the last course of ACTH and in a state of relapse, he was rehospitalized and treated with Concentrated Adrenal Cortex Extract intramuscularly in the above-mentioned dosage. Changes in his ventilation studies and level of peripheral blood eosinophils are shown in Figure 3. A gradual improvement in the severity of his asthma occurred while he was receiving adrenal cortex extract, but his chest was never completely free of râles and he continued to require symptomatic measures for the relief of wheezing. Asthma of the former degree of severity re-

curred on the third day following the cessation of therapy, coincident with a return of his former level of blood eosinophilia.

This patient has subsequently responded to an additional course of 225.0 mg. of ACTH in a manner comparable to that of his initial two courses, as previously described.[8]

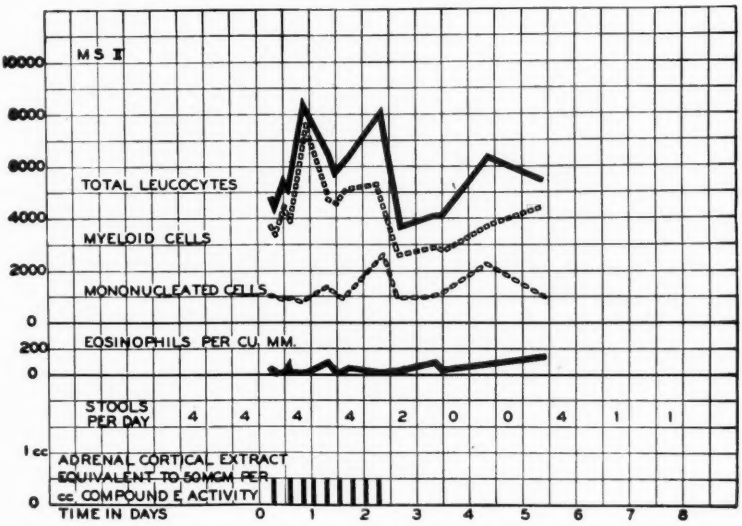

Fig. 4. Variations in the cellular elements of the peripheral blood as determined by glycol-stain counting chamber differential technique and the symptom response in M. S., a patient with gastrointestinal allergy, following treatment with Concentrated Adrenal Cortex Extract.

Case 4.—M. S., a woman, aged thirty-eight, had been under observation for three years with a diagnosis of gastrointestinal allergy. She was known to be highly sensitive to wheat in that its ingestion either accidentally or as a result of deliberate test feedings produced acute abdominal cramps and diarrhea requiring hospitalization. In August, 1949, this patient developed a recurrence of abdominal cramps and acute diarrhea having the characteristics of her previous attacks in spite of avoiding known allergenic foods. On the assumption that she had developed a spread of sensitivity to other articles of the diet, she was hospitalized and treated with 325.0 mg. ACTH in 25.0 mg. doses every six hours. On admission she was having between four and six liquid stools daily. Her diarrhea and other abdominal symptoms ceased after forty-eight hours of ACTH therapy. The day following this course of treatment she was returned to a general diet, including repeated doses of wheat, which she tolerated without a recurrence of her abdominal symptoms. She remained symptom-free on a general diet for a period of two weeks, then had a recurrence of diarrhea which was controlled for another week as a result of specific food avoidance. In spite of continued dietary measures she had a recurrence of abdominal cramps and diarrhea in the fourth week. She was then given nine doses of 0.5 c.c. each of Concentrated Adrenal Cortex Extract intramuscularly over a period of two days, as indicated in Figure 4.

Her abdominal cramps and diarrhea subsided by the end of the second day of therapy, and aside from a transient recurrence of diarrhea three days after cessation of treatment she remained symptom-free for the following two weeks even though

continuing to follow a general unrestricted diet. By the end of three weeks her gastrointestinal symptoms had recurred in their former severity and again were not controlled by the avoidance of wheat and the frequent use of aminophylline. In the past she had obtained a greater degree of relief of her severe abdominal pain as a result of the administration of aminophylline intravenously than from any other type of symptomatic therapy.

DISCUSSION

Although the intramuscular administration of Concentrated Adrenal Cortex Extract is effective in bringing about a marked diminution of the circulating eosinophils in a manner similar to that following the administration of pituitary adrenocorticotropic hormone (ACTH), it is far less effective than ACTH in relieving the symptoms of chronic bronchial asthma. When given in large doses over a period of several days, Concentrated Adrenal Cortex Extract was slightly more effective than when administered for shorter periods, but in the one case in which this dosage schedule was tried it resulted in partial relief of asthma only during the period of administration. This agent seemed to be relatively more effective in bringing about relief of gastrointestinal allergic symptoms in the single case in which it was tried.

The relative failure of highly potent adrenal cortex extracts to relieve the symptoms of bronchial asthma when this condition may ordinarily be treated effectively by means of pituitary adrenocorticotropic hormone (ACTH)[8] and Cortisone[9] is an interesting point for speculation. Selye[13] has pointed out an apparent antagonism between the gluco-corticoids and the mineralo-corticoids. The injection of formalin in the hind paw of a rat in the presence of an excess of mineralo-corticoids (desoxycorticosterone acetate) produces experimental "formalin arthritis." The development of this reaction may be inhibited by treatment with ACTH or Cortisone. Selye[14] further pointed out that some adrenal cortex extracts are rich in gluco-corticoids but they also contain mineralo-corticoids. In as much as adrenocorticotropic hormone (ACTH) seems to stimulate the production of relatively more gluco-corticoids than mineralo-corticoids and Cortisone is a naturally occurring gluco-corticoid, the relief of allergic symptoms, including rheumatoid arthritis, with ACTH or Cortisone therapy may be the result of increasing the gluco-corticoid effect to counterbalance that of the mineralo-corticoids.

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(Continued on Page 187)

THE RELATION OF ALLERGY TO CHARACTER PROBLEMS IN CHILDREN

A Survey

T. WOOD CLARKE, M.D., F.A.C.A., F.I.A.A.
Utica, New York

FIVE years ago a boy fifteen years of age was referred to me by the late Dr. Richard H. Hutchings, past president of the American Psychiatric Society and editor of the *Psychiatric Quarterly*. The boy had been sent to him with the expectation of placing him in a state hospital for mental diseases.

This boy, previously happy and amenable, had, for three years, suffered from attacks of acute excitement in which he would rage around the house smashing china and furniture. The attacks lasted about thirty minutes and usually were followed by sleep. He had had five such outbreaks in the five weeks before I saw him. The family had endured it to the limit of their endurance and had decided that he was a subject for a mental hospital.

Dr. Hutchings, in taking his history, found that he had had eczema as a child, and four years before had developed hay fever and asthma, which had lasted for two years. He had had no symptoms of allergic diseases for the last two years. However, as Dr. Hutchings was interested in the work I had done in his hospital on allergy in epileptics, and had published an article of mine on "Allergy of the Central Nervous System," he referred the boy to me.

Physical and neurological findings were not significant.

The first day's testing however showed 4+ reactions to oat and wheat. Later he reacted to feathers, fall pollens, cat dander, house dust and slightly to other foods. Oat and wheat were removed from his diet, and later desensitization inoculations were given for the inhalants.

The results of removing the oat and wheat from his diet were dramatic in the extreme. Almost overnight the boy's entire character changed. From being unhappy and apprehensive he became, in a very few days, happy and co-operative. He has had no outbreaks of temper for five years. He is friendly and full of fun. He is now doing well in college. This case—with that of a woman who had been admitted to the Marcy State Hospital some dozen times for episodic mental disorder and who at last said that she thought these were in some way associated with her asthma, who gave a strong reaction to dog hair and had a relapse of her psychiatric condition when a dog was brought into the ward—and that of a morose boy, who had been expelled from four schools as incorrigible, who cleared up emotionally when the foods to which he was allergic were eliminated, got good marks in school and became an enthusiastic Boy Scout—set me to wondering

Since the circulations of the two journals do not conflict, this article is also appearing in the current issue of *Psychiatric Quarterly* by mutual consent.

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Dr. Clarke is consulting allergist, Marcy State Hospital.

whether some of the mental changes which occur in what we designate as problem children might not be the direct result of an allergic cerebral edema such as we get in migraine and epilepsy of allergic origin, or of the chronic abnormal vasomotor activity of the cerebral vessels due to the constant allergic reaction resulting from eating some food or breathing some inhalant to which the "problem child" is allergic.

At the 1949 annual meeting of the American College of Allergists the matter was discussed with a number of the officers of the College. They were unanimously of the opinion that it was a subject worthy of systematic study. As I had been serving the College for five years as a member of the faculty of its instruction courses as lecturer on allergy of the central nervous system, it was agreed that I should investigate the subject for a year and report my findings at the next meeting of the College in January, 1950.

Very little attention has been paid to the relations of allergy to character in the medical literature. The first extensive articles on the subject were written in 1922 and 1924 by W. Ray Shannon[12] so long ago that allergy is referred to as anaphylaxis and the allergic diseases as sequels of the exudative diathesis. He described four children with allergic diseases and the "neurotic diathesis": one with allergic history, no present allergic symptoms, but great restlessness, and two with marked nervousness but no other manifestations or history of allergy, all of whom had positive skin reactions to foods. All seven of these lost all nervous symptoms as soon as the offending foods were removed from their diet.

Brief mention is made of psychological changes in allergic patients in articles by Hoobler,[4] Kahn,[6] Duke,[3] Randolph,[10] Rowe,[11] Clarke,[1] and Winkelman and Moore,[13] and more recently in the splendid article on cerebral allergy by Davison.[2] The textbooks usually give only a few lines to the subject.

In order to get a consensus of opinion of my allergist confreres on this subject, I sent a letter to all the allergists of the United States and Canada listed in "The Directory of Physicians Interested in Clinical Allergy" asking for their experiences with allergy causing deleterious character changes in children which cleared up when the allergic conditions were brought under control.

The response to these letters has been most gratifying. In all, 171 replies have been received. Of these, nine expressed the belief that allergy had nothing to do with personality, seven took the attitude that allergy was psychosomatic, that the allergy was the result of emotional conflict which made the patients problem children, fifty-eight said that either they took no children or had not had their attention called to psychic complications of allergy, and ninety-five assured me that they had noticed personality changes due to allergy which corrected themselves when the allergic element was eliminated. Many said that they had been thinking along the same line, assured me that they thought I was on the right track, and that

calling attention to the relationship would be of value to both allergists and child psychiatrists. A few opinions are quoted:

"As you know, I have emphasized the psychological changes and effects on the nervous system in children due to chronic allergy for many years." (Albert H. Rowe, M.D.)[9]

"So often during the first visit no mention is made of the child's behavior, and the only concern with the parents is the presenting allergic symptoms. However, when the allergic situation has been brought under control, it is amazing how much emphasis is placed by the parents upon the altered behavior of the child. The stock phrase that is heard frequently is, 'He is a different child to live with.'" (Frank F. A. Rawling, M.D.)[9]

"I have seen a number of children in whom the correction or improvement of the allergy has been followed by definite lessening of the emotional instability and by better behavior." (Louis Tuft, M.D.)[9]

"There is no doubt in the mind of any physician who is practicing allergy that food sensitivities do bring about definite changes in children's behavior." (Abraham Colmes, M.D.)[9]

"On a number of occasions I have noted behavior problems occasionally of severe degree in children who are unquestionably allergic. I have found not infrequently that the behavior has improved to a marked degree when the allergy was controlled." (C. R. K. Johnston, M.D.)[9]

"It has been my observation for a long time that quite a large percentage of allergic children who come to me have considerable irritability and many of them are so-called problem children. Furthermore, the lessening of the irritability, and the greater ease with which these children are managed, closely parallels the improvement in the specific allergic condition for which they are being treated." (Gerald C. Grout, M.D.)[9]

"I certainly agree with your original premise regarding character changes in children suffering from allergic problems. One of the most pleasing and notable things in the treatment of children is this change for the better in their personal attitude and characteristics. One of my routine questions is asking mothers about this, and invariably the answer is that the child is physically better but tremendously improved in disposition, eating habits, sleeping, and general amiability." (Martyn A. Vickers, M.D.)[9]

"It is my impression and the impression spontaneously expressed by their parents that several small children who were excessively talkative, volatile and excitable have been quieter, more placid and much easier to care for after their allergies were brought under control." (Edna S. Pennington, M.D.)[9]

"A number of the children we see with asthma and perennial vasomotor rhinitis are often irritable, fussy, and difficult to manage. These symptoms improve as the allergy diseases mentioned are brought under control." (G. B. Logan, M.D.)[9]

"There have been numerous children who have been patients of mine that have been called problems by their parents, and after their allergies have been corrected the parents have remarked that there is all the difference in the world." (Katharine Baylis MacInnis, M.D.)[9]

"I am convinced that a considerable number of so-called problem children are allergic and that correction of this state of affairs will go a long way towards eliminating these undesirable characteristics." (John P. Henry, M.D.)[9]

"My experience has been that in quite a few children and during their allergic flareups, particularly asthma, there is a distinct psychic problem where the child is difficult to handle. As the condition is corrected or relieved, the patient's personality, his behavior, et cetera, change entirely for the better." (Sim Hulsey, M.D.)[9]

"Practically every day since I have been practicing allergy, mothers come in with

the statement that 'Johnny is so irritable', or 'his disposition is so much better since he is on his diet', or that 'he is as mean as the devil when he eats a certain food.'" (Fannie Lou Leney, M.D.)[9]

"My most pertinent observation in this matter is that when a child is sent to us for allergy study who is in school, I find the grades, much of which you know is based upon adaptability, may be low. After a semester or a year of allergy control, these youngsters make a distinct rise in their class standing." (William A. Thornhill, M.D.)[9]

"Certainly anyone who has followed children's allergic troubles and their improvement under treatment has been impressed by this part of the problem. Certainly allergic management of the children makes a great difference for the better in their personalities and relations to other pupils." (John F. Pilcher, M.D.)[9]

"I have had mothers tell me that their children seem to be less irritable and better adjusted to school environment when their allergies are under control." (S. C. Missal, M.D.)[9]

"We have had frequent cases of children with asthma in which we have had appreciative mothers say, 'I also am so happy that he (or she) is an entirely different child and is much more like other children. He is not so irritable; he is now a happy child.'" (Fred C. Endres, M.D.)[9]

Of these ninety-five allergists, forty sent me brief histories of 122 cases from their own experiences. Most of the others said that they had many times had cases in point, but as they did not have their files cross-indexed with this in mind they could not send me case reports.

In the 122 cases reported to me, the types of characteristics which were relieved by eliminating the allergy factor varied greatly. The most common reports were of irritable, fretful, quarrelsome children, who could not get along with others, often had to be taken out of school as they upset the classes and were considered incorrigible, who, after the nature of their allergy was discovered and proper steps taken to correct it, became friendly and happy and took active and joyous part in the occupations of their mates.

A few representative cases of the various types are reported briefly:

Case 1.—Age ten years. First seen with a history of cough, unexplained abdominal distress daily and irritability with some personality change over a period of four or five years. Intradermal skin studies showed positive reactions to several of the more common foods, principally corn, wheat, chocolate and orange. Gradual improvement followed avoidance of the offending allergens and at the time of the last visit on June 2, 1949, the patient was symptom-free. The patient's mother stated that it was difficult for her to believe, but she had finally been convinced that the complete reversal in the child's attitude and loss of irritability had accompanied improvement in the allergic symptoms. She further stated that prior to allergic management the child had never smiled and that now he is a very happy child. (Gerald C. Grout, M.D.)[9]

Case 2.—Age three years. A white male child had been seen by his pediatrician who felt that he had celiac disease because of his frequent large movements. His mother stated that his behavior was peculiar, that he would at times "act crazy." He cried almost constantly for the first eighteen months of his life. He was extremely irritable and highly excited. He had a hoarseness that would come and go. On the basis of the history, we placed him on an elimination diet, eliminating milk, wheat and eggs and many of the other commonly incriminating allergenic foods,

and he made sensational progress. We found him definitely sensitive to rice, milk and to a lesser extent wheat, and when these foods were included in his diet one could precipitate the old symptoms of excitement and bizarre behavior. He had been watched since 1946 and he has gradually improved. (Carl L. Mauser, M.D.)[9]

Case 3.—Age five years. Complaint: recurrent bronchitis, hay fever. Diagnosis: bronchial asthma. This five-year-old child was a typical allergically-ill child, thin, nervous, restless, irritable, unco-operative, unhappy. He had been withdrawn from nursery school during the past year because he was a "trouble-maker." The usual treatment was followed: removal of offending allergens, hyposensitization with house dust year round and prophylactic treatment with mixed ragweed pollen extracts. The results were quite spectacular in that this child has had no asthma since September, 1943. Rapid gain in weight, stamina and emotional stability occurred, and the child entered first grade in the fall of 1943 and has done very well. The boy is now a normal, happy, co-operative and pleasant child. (Arthur G. Baker, M.D.)[9]

Case 4.—A child two years old had atopic dermatitis, nervousness, irritability, and restlessness, and frequently awakened at night crying. This child is allergic to several foods. The eruption is improving, and the disposition parallels the eruption as far as improvement is concerned. When allergenic foods have been added to the diet, the skin eruption and the cerebral symptoms have been aggravated at the same time. (Milton Millman, M.D.)[9]

Case 5.—Age three and one-half years. Diagnosis: infantile eczema and mild perennial hay fever in July, 1946. A diagnosis of asthma was made in December, 1948. This child was extremely irritable, "spoiled," and the parents had an exceedingly difficult time in toilet training her. It was found that the eating of peanuts was the food which was responsible for her being extremely cross and irritable and difficult to control. Other foods were found to produce eczema and still others contributed toward asthma and hay fever. The omission of the offending foods resulted in a happy child, easily controlled. (George W. Owen, M.D.)[9]

Case 6.—An eleven-year-old white boy, an only child, had asthma for the past four years, worse at night. He had received numerous treatments, including penicillin, without any apparent benefit. Allergic skin studies were done. He was immunized against the inhalant factors, particularly house dust. Removal of the positive foods from his diet, namely celery, cauliflower, peas, citrus fruit, oatmeal and chocolate was carried out. He has shown remarkable improvement in his allergic condition, and his mother has also noted a considerable degree of improvement in his behavior. He was irritable, stubborn, rowdy and introverted. Since the institution of treatment and the elimination of the positive foods, the child has been free of his asthma, has shown a great degree of co-operation with his parents, his schoolwork has improved and in addition he has regained his friends. (James H. Putnam, M.D.)[9]

Other children were described as antagonistic, negativistic, and stubborn, youngsters whom nothing pleased, who refused to follow suggestions and went into rages when their slightest wish was ungratified, but who, when their allergies were corrected, became amenable, obedient and docile.

Case 7.—Age six and one-half years. Came in because of a perennial and seasonal hay fever. She was also emotionally upset, unco-operative and was considered to be a badly spoiled child. Tests revealed a sensitivity to ragweed pollen, grasses, and oak. Under perennial treatment the hay fever was well controlled, and she is now very co-operative and normal emotionally. (Samuel J. Taub, M.D.)[9]

Case 8.—Age five years. White female child. First seen April 28, 1948, because of chronic cough, asthma, nasal allergy. She was placed on an anti-allergenic regime which included hyposensitization therapy. This youngster was frequently a marked problem at home. She would spit in the mother's face, kick her and would not obey either parent. She was contrary to all suggestions, and there was a great sleeping problem. She has improved remarkedly both from an allergic standpoint and with regard to her disposition. Although she is not completely over her bad habits, there is definite improvement. (Carl L. Mauser, M.D.)[9]

Case 9.—Age six years, "nervous" all his life. Examination showed an eczema of the rectum. But the most outstanding item was a compulsive type of behavior problem, the child screaming, not from fear, but from anger, fighting, kicking, trying to destroy property, and all the time swearing and cursing vociferously, enunciated at the top of his voice in baby talk that was so indistinct I hoped the nurses did not understand what he was saying. The mother told me they had completely lost control of the boy. Punishment was of no avail. He was placed on an elimination diet. Immediately his instability quieted, his rectum healed, he was well behaved and cooperative on visits to the office. The addition of milk to his diet caused immediate reversal of his behavior problem, and the rectum began to hurt. With the removal of milk he again became quiet and well behaved. A second test gave the same results. (J. G. Little, M.D.)[9]

Others were boisterous, talking incessantly and over-loudly, constantly hyperkinetic, and inclined to be destructive, who, after adequate treatment, became gentle, respectful and quiet.

Case 10.—Age six and one-half years. Reported on April 6, 1949, with chief complaint of dry skin, stuffy nose and asthma on a few occasions. On intradermal testing he gave reactions to pollens (grass and ragweed) and many inhalants. He is being desensitized to the pollens, and to the inhalants with satisfactory results. The child is bright in school, hypersensitive, irritable, and strong-willed, and talks constantly, with a tendency to stutter. Since we started treatment the mother says that he stutters less, is greatly improved in his behavior, less irritable, and listens more attentively to his mother. (Saul W. Chester, M.D.)[9]

Case 11.—Child began during the first year of his life with nasal obstruction and drainage involving the nose and ears, continuing along throughout the winters. Later he had vomiting and coughing spells. At the age of four these were controlled with pollens and elimination of a few foods. He first reported at the age of six in 1945 during the early winter. Bacterials and house dust were used during the winters and pollens throughout the summers. Throughout the course of the three years that he was treated in the office he showed the widest imaginable personality changes. When he was under control, he came in and took his shots and left without any argument, but when he would slip, or when a new offender showed up, it would be almost impossible to retest or even give him his regular shots. This happened several times. "He varied from the most angelic to the most obstreperous child that I ever saw, depending on the degree of control that we had over the allergies." His school record and his association with other children went along with our experiences in the office. (W. H. Woern, M.D.)[9]

Case 12.—Age seventeen years. Asthma, allergic dermatitis; pale, undernourished, weight 85 pounds. She was generally disliked by her family, and two years previous to admittance had picked a saucepan from the stove and hurled the contents in her

mother's face. She had eczema since infancy and many attacks of croup. She was three years retarded in her school work and was found to be sensitive to cat, dog, and horse hair and lactalbumin. Under treatment since August 1945, she has been free from her eczema and asthma without booster shots oftener than twenty-two to twenty-eight days. Her weight has increased 15 to 20 pounds, and personality changes have been such that she is no longer disliked at home. (C. A. Buck, M.D.)[9]

Case 13.—A boy of four and one-half years with bronchial asthma since seventeen months of age, allergic rhinitis (perennial and seasonal), probable gastro-intestinal allergy, history of infantile eczema. He was an extremely nervous, hyperactive, undernourished child with a high-pitched, strident voice, demanding attention. When allergic symptoms were controlled by diet, elimination of reacting inhalants in the home, and desensitization to molds and ragweed, the child became much quieter, more reasonable, less demanding, and his voice lost the strident quality and became calmer and lower in pitch. Although he still remained a very active youngster, he slept well except during periods when the molds were bad, his appetite improved, and he learned to eat many foods he would not taste before. In the first six months of allergic management he gained four pounds and in the second six months 7 pounds. (Louise O. Kappes, M.D.)[9]

A number of the children were described as bashful and timid, children who would cling to their mothers' skirts and weep if spoken to, who were marked introverts, depressed, always tired and without ambition. These children, after the allergy factor was removed, became extroverts, friendly and vigorous in their play.

Case 14.—Age eight years. Began his treatments September 1948, for an almost persistent sore throat and cold over the years. He was also a timid, very mild-mannered child who cried on the least provocation and objected to having anything done in the way of treatment. He was started with pollens and bacterials and carried throughout the winter with very nice relief until February of 1949 when he again began having these crying spells and got his feelings hurt at the most trifling things. House dust was added, and he immediately lost his symptoms until March 15 when they returned. Bermuda grass pollens were added and he again lost his complaints. At the present time he is a cheerful, well-behaved child who can get along with other children. (W. H. Woern, M.D.)[9]

Case 15.—An eight-year-old girl with typical, although fairly mild, recurring bronchial asthma and allergic rhinopathy. There was also rather chronic coughing between attacks. Allergic survey including environmental tests and elimination techniques proved the allergens to be house dust, animal danders, pollens and other inhalants. Foods were not shown to be significant. The patient was troubled by periods of obvious depression, unexplained spells of crying, and evidence of introversion. Appropriate allergic therapy completely eliminated asthmatic attacks and produced a marked improvement in the nasal symptoms and recurring cough. At the same time most, though not all, of the psychic disturbances disappeared. For example the child no longer cried or sat around unmoving for long periods of time. (Philip M. Gottlieb, M.D.)[9]

It has been interesting to see the number of cases reported in which children, who, owing to inattentiveness, have been problems to their teachers and have been obliged to repeat their grades, who, when their allergy

has come under control, have made startling improvement, not only in their scholastic standing but also in their school behavior. The listless have become active, the inattentive good students.

Case 16.—A boy, aged six years, whose allergy consisted of an allergic bronchitis with a questionable psychogenic factor, and a questionable perennial allergic rhinitis. His grades in school had not been satisfactory; he was irritable and showed other deviations from normal behavior. After his allergy was controlled on treatment, it was noted that his grades were definitely improved, he had a much better disposition and behavior, and it was felt that these changes in disposition were associated with control of his allergic problem. (C. R. K. Johnston, M.D.)[9]

Case 17.—A girl of nine years whose allergic symptoms included migraine, constipation, and frequent "colds." She lost thirty-five days of school from illness in 1947-1948. Despite an I.Q. of 140, her schoolwork was not entirely satisfactory. She made frequent mistakes in copying. She was "difficult" for her teachers, had a chip-on-shoulder attitude and imagined her classmates did not like her. Her pulse-accelerating food-allergens are tomato, cheese, pork, banana, mint and licorice. After all of these foods had been eliminated from her diet, her schoolwork has improved and her attitude toward teachers and classmates has become normal. She has lost only one school day in the past year from illness. Has a "cold" now only within two days after exposure to one of her food allergens. (Arthur F. Coca, M.D.)[9]

Case 18.—A six and one-half-year-old boy with spring and fall hay fever and a milder perennial allergic rhinopathy with cough. The patient was doing poorly in school, was antagonistic to his parents and often negativistic in emotional situations. Dust proofing of the bedroom and hyposensitization with pollens made, in the parents' own words, "a new boy of him." His schoolwork improved markedly so that he became one of the better pupils in the class, and the relationship with his parents showed improvement little short of amazing. (Philip M. Gottlieb, M.D.)[9]

Case 19.—A boy of nineteen years had nasal blocking and discharge for one year and frequent dull frontal headaches. He had been attending a Polytechnical High School for five months and was unable to concentrate. He was found allergic to milk, wheat, yeast, feathers, house dust and a few other foods. He felt much better in two months on allergic diet and removal of feather pillows. Desensitization to wheat, yeast, and milk was undertaken because he found it so hard to eliminate these when living in a dormitory. In January, 1948, after one year of allergic regime, he reported that, whereas before the allergy tests were done he had flunked out in school twice, the last quarter he had made four A's. In another year he was graduated with honors and was accepted at one of the most difficult technological colleges to enter in the country. (Louise O. Kappes, M.D.)[9]

Case 20.—Age thirteen. This boy came to the office because of chronic sinus difficulty. In the course of taking the history the parents who were both present related the boy's mental sluggishness, retardation and inability to grasp his studies at school so that private tutors were necessary. He failed to make friends, was a good deal by himself and never enjoyed the usual games indulged in by boys of his age. Studies revealed the presence of pollen disease, particularly ragweed and also sensitivity to milk. The latter diagnosis was based chiefly upon a positive reaction to milk. The boy was put on pollen therapy, allergic cleanliness was instituted in his environment and milk in all forms was omitted from the diet. Within a week the mother reported that there had been a marked improvement in the nasal condition, and incidentally she remarked, "Somehow the boy is grasping his studies a little better and he seems

more companionable." Within another two weeks the tutor suggested that the boy return to school, and thereafter his studies were uninterrupted and school days were welcome to him. He commenced to encourage the friendship of other boys of his age, soon developed interest in baseball and started to lead a well-rounded life of studies and physical activities. The mother, unknown to the teachers of the school, introduced milk over a trial period and within two days the school reported that the boy was slipping again. He was again dull and his perceptivity was lessened, and he seemingly was headed for the same condition he was in before treatment was instituted. The omission of milk promptly relieved all the symptoms and thereafter the boy has made an uneventful recovery with the aid of pollen treatment. (Abraham Colmes, M.D.)[9]

Restlessness at night, crying out in sleep, nightmares, and enuresis have all been reported as disappearing with control of the allergy.

Various explanations have been given for these untoward characteristics in allergic children. Some are convinced that the constant, or recurrent, discomfort from the itching of eczema, or the respiratory difficulty in asthma so affect the child's stability that his mental equilibrium is broken down and his character changed. This is undoubtedly one cause of the condition, and the relief from the discomfort relieves the tension on his nervous system.

In many cases, also, over-solicitous parents, in order to compensate for their child's illness, and its consequent suffering, misguidedly remove all control over him and endeavor to see that his slightest and most unreasonable wish is promptly gratified. This attitude invariably ends in the little patient becoming arrogant, demanding, unhappy and furious when his desires are in any way thwarted. This is certainly an important element in the problem.

It has been interesting, on the other hand, to see how many of the reports received have stated that the writers have for long believed that in many of their patients there is a deeper, more intrinsic cause for the personality changes which their patients show, that there is some definite allergic reaction in the brain.

It is well established that a cerebral edema due to an allergic reaction in the brain tissue, or meninges, can be severe enough to cause migraine headaches,[5,8] or convulsions[7] usually classified as epilepsy. It is easy to imagine a situation where a reaction resembling giant hives in the cerebrum could cause emotional responses which would change the normal child into an uncontrolled brat. Sudden increase of intracranial pressure, which we know can occur from allergy, might well be the underlying cause of a temper tantrum, of over-excitement, or of any of the other psychic reactions with which we are so familiar in allergic children, and which are so dramatically described in the many letters I have received from the allergists of the United States and Canada.

In these letters I have received descriptions of children who, while they were allergic, showed none of the usual symptoms of the condition or were not suffering enough from them to account for their personality problems,

still had such problems in severe form, and were relieved of them when the allergic factor was removed.

Case 21.—A girl of twelve years of age was referred because a cousin's disposition had improved markedly when an allergic condition had been cleared up. This girl showed no recognizable allergenic manifestations but had become such a problem that the mother said "she and her father can no longer live in the same house." An allergy study was made and the child was found to be sensitive to beets and asparagus. Asparagus was rarely eaten and could be disregarded. But it was found that she daily ate an ice cream cone made with beet sugar. When beets were stopped and the daily ice cream cone changed to one without beet sugar the change in this child "was of such a nature that one would have to be around the patient to appreciate the influence of the beet allergy on her personality." A ten-year follow-up on this case has shown her developing in a normal manner. (Herbert J. Rinkel, M.D.)[9]

Case 22.—A schoolgirl, aged ten, had become a severe behavior problem, and her mother was at her wits end to know what to do with her. The child was exceedingly unruly. She would lie in bed and refuse to get up. She whined continuously and complained of transient abdominal pains. She would not go to school for weeks at a time, and she became more and more irritable. Although she showed none of the usual manifestations of allergy, unless the abdominal pains were due to a gastrointestinal allergy, she was referred for a study. A complete physical and laboratory examination was entirely negative. Careful review of her dietary habits revealed that she was eating large quantities of chocolate. Allergic investigation showed marked sensitivity on cutaneous testing to chocolate and several other common foods. The offending foods were withdrawn from her diet with complete alleviation of her symptoms. The foods were returned again one at a time until she was given chocolate, at which time her symptoms returned. Chocolate and cocoa in all forms were immediately removed from her diet, and since then the child has been well and happy and makes no objection to going to school (E. L. Grinnell, M.D.)[9]

Case 23.—A five-year-old boy was referred by a pediatrician because of coughing, sneezing, post-nasal drip throughout the year, worse in the spring and fall. The child was nervous, irritable, easily upset, inclined to whine or cry at little things. Following allergic management which included allergic diet, removal of feathers, and dust precautions, desensitization to molds, ragweed, and grass, his disposition improved a great deal and his sneezing, sniffling, and coughing ceased. He became a happy, co-operative child. His father remarked, after the child had been under treatment for a year and a half, that he could tell when the boy needed a mold injection by a change in dispostion before any nasal symptoms started. (Louise O. Kappes, M.D.)[9]

Case 24.—This boy, the son of an allergist, at the age of eight had frequent hives and at times slight nasal allergy and gastric-intestinal symptoms believed due to drinking milk. He was found to be allergic to milk and eggs. Later it was found that when this boy touched milk he manifested symptoms. He would immediately become very sleepy and would have to lie down and sleep. Upon awakening his eyeballs were very bloodshot and he felt very groggy. This was a great handicap to him in going through college because if he touched any milk he would not be able to study that evening, and it was necessary for him to remain out of college one semester in order to stabilize himself and get on to a special diet. On returning he did not return to his fraternity house but lived outside and boarded in a cafeteria where he could select his own food. The action of eggs on this boy was just the opposite. Instead of being lethargic it apparently made him nervous and he could not concentrate on his mental work but was more apt to go to the shop and begin

working with his hands and busying himself in that way. There was a definite difference in those two foods. At the present time, which is about fifteen years later, he has been able to eat eggs but still has to avoid milk in any form. (H. D. Parkhurst, M.D.)[9]

The lad I reported on at the beginning of this paper illustrates this situation. He had had no physical evidence of his allergy for several years and between attacks appeared quite normal except for his anxiety over his outbreaks. His family had not pampered him. Can one account for his temper outbursts better than by a sudden increase of intracranial pressure, or a cerebral vasomotor abnormality? The immediate disappearance of the outbreaks on removing the oat and wheat from his diet is certainly evidence that they were of an allergic nature.

Allergy is selective. In one person it can affect the skin and no other region. In another it will light upon the bronchial tubes alone. In others the nose, the eyes, the ears, or the gastrointestinal tract may be solely involved. We know that it can affect the motor areas of the brain and cause convulsions, or paralyses, or other areas and produce migraine. Is it too much to imagine that it can strike the psychic centers in the frontal lobes, and these centers alone, and cause character changes? Such character changes, due to an allergic reaction, can well result in the making of a "problem child."

The "problem child" rarely has a pleasant life. He is punished for being naughty and disobedient. He has a difficult time in school, is disliked by his teachers and hated and tormented by his schoolmates. If his characteristics are due simply to a mean and selfish nature, he may get his just deserts: if they are due to faulty home training, his parents certainly get theirs. If, on the other hand, they are the result of a mental illness, he deserves great sympathy and every possible effort to correct the underlying physical or mental cause. If the cause is an allergic reaction either in the brain or in any other part of the body, he deserves a thorough allergy study. A little time spent on this may change the whole course of a child's life. Allergy tests and appropriate treatment may be far more effective than either beatings or other forms of punishment.

The "problem child" frequently grows up to be a normal, although often an erratic, adult. He may, however, end up as a true psychotic. Today some of our state hospitals are erecting separate buildings for the care of "problem children" in the hope that by their early treatment the psychic seeds may be rooted out and future psychoses forestalled. If every child who has to be sent to a state hospital, or every "problem child" seen in our offices, or child guidance clinics, could be given a thorough allergy study, it is not too much to hope that some, perhaps many, would be found to be allergic, could have their allergy treated and could be returned to their homes normal emotionally as well as physically. The boy I reported at the opening of this paper appeared to be on the straight road to insanity. Dr. Hutchings' appreciation of the influence of allergy on the central

nervous system may possibly have saved this lad from a violent ward of a state hospital.

If allergists would pay more attention to the psyche of their child patients, if child psychiatrists would appreciate that psychosomatic medicine can travel in reverse gear, that physical allergy of the brain can cause emotional changes, and if the two would co-operate in the study of the "problem child" from both the allergic and psychic angles, we may well hope that our state hospitals may not need such extensive facilities for the care of children, that many children may cease to be problems, and fewer adults become psychotic. The subject is deserving of systematic study.

Acknowledgment

The author wishes to express his sincere thanks to the many allergists who have made this survey and paper possible by their co-operation in expressing their thoughts on the question and reporting their cases.

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7 Cottage Place

DISCUSSION

DR. HAL M. DAVISON, Atlanta, Georgia.—Just as in the case of most other physicians, for a time I considered mental and emotional symptoms occurring in allergic patients to be either a coincidence or secondary symptoms caused by the discomfort of the disease. The fact that following appropriate treatment these symptoms and the allergic symptoms disappeared together ruled out the first possibility. The fact that the mental and emotional symptoms occurred at times without other known allergic symptoms, and that they could be reproduced at will by feeding certain foods without producing other allergic symptoms, ruled out both the first and second possibilities.

Dr. Clarke's paper removes any possible doubt that these symptoms must be considered the direct result of allergic reactions in the central nervous system. Bray, a pediatrician of London, was one of the first to describe personality changes in chil-

dren due to food sensitivity. Dr. Clarke has referred to other writers and has given you reports from many other physicians. These children, without the foods in their diet and with the foods in their diet, are literally Dr. Jekyll and Mr. Hyde. Their parents are equally pleased and astonished by the improvement in the patient following allergic management.

In the paper, "Cerebral Allergy," referred to by Dr. Clarke, we reported eighty-seven patients, five of whom were in the first decade of life and eleven in the second. The remaining seventy-one were scattered through practically all ages above twenty. The symptoms in adults and in the youngsters varied very little. We wish to stress the following:

Sleepiness on the one hand and insomnia on the other.
Sluggish thinking, inability to concentrate.
Childish compulsions.
Sense of unreality, as if patient were living in a dream.
Inability to be pleased about anything.
General unhappiness.
Morbid depression.
Loss of pride.
Loss of interest in the other sex.

I hope that Dr. Clarke will continue his observations along these lines, not only in children but in adults. I wish to stress again the fact that it now appears that practically any symptoms in humans may be caused by allergic reactions, and that when we have a symptom we cannot demonstrate any other cause for, we should think of allergy. Also, when we have symptoms occurring in patients who have other allergic manifestations, or a strong family history of allergy, we should always consider allergic reactions as a possible cause of their trouble.

In closing, I wish to quote the remark of one of my patients: "It is easy for me to follow your philosophy of life when I am on a diet, but impossible when I am not."

CONCENTRATED ADRENAL CORTEX EXTRACT

(Continued from Page 174)

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CERTAIN VASCULAR EFFECTS OF HISTAMINE AND d-TUBOCURARINE IN MULTIPLE SCLEROSIS

Part III

HINTON D. JONEZ, M.D., F.A.C.A.
Tacoma, Washington

THE theory that multiple sclerosis is a disease of allergy[14,17,29,31,34,38,39,40] has been gaining acceptance to a great extent during the last few years. Dr. Tracy Putnam, Chairman of the Medical Advisory Board, National Multiple Sclerosis Society, stated before a United States Senate Committee on May 10, 1949, in part: ". . . At last we began to have some tangible facts about multiple sclerosis. Its allergic origin, at least in some cases, was confirmed."

In the Multiple Sclerosis Clinic at St. Joseph's Hospital,[27,28] we have been treating this disease as one of allergy for the past three years.

Histamine diphosphate is given for hyposensitization[15,37] and vasodilatation.[10,16,19,23,42] d-Tubocurarine chloride in oil and wax is used to aid in the control of spasticities, also as an adjunct in muscle re-education. Lately we have added vitamin B_{12} to our therapy.

The methods of Horton[5,24,25,26,33,34,36] are used for subcutaneous and intravenous[11] administration of histamine. For the past year patients on leaving the clinic for home have been placed on histamine iontophoresis by self-administration, using the technique as described by Abramson.[2,3,4]

The question arose as to the length of time of the pharmacological action of histamine by the various methods of its administration. We know that histamine is a normal constituent of blood,[30] the concentration in human blood being from 1 to 8 micrograms per 100 c.c.[8] However, artificially introduced histamine cannot be traced in the blood or urine since it is rapidly destroyed by a blood ferment, histase.[1] At our clinic we noted that venous blood when drawn while histamine was being injected was redder and more arterial-like in appearance. This observation suggested that a quantitative study of the oxygen content of the blood be made. In 1944 Peters, Horton and Boothby[34] had shown an increase in oxygen consumption during intravenous histamine injection (Van Slyke gasometric method). Also, in 1947 Grob, Lilienthal and Harvey[21] reported measuring the histamine-like effects of an aqueous solution of curare by blood oxygen content (method not stated). The results of our studies are shown by Tables I to VIII.

TABLES

The oxygen content determinations of the venous blood in the following tables were performed by the volumetric method of Van Slyke and Stadie,

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TABLE I. 2.75 MG. HISTAMINE DIPHOSPHATE IN 250 C.C. NORMAL SALINE, INTRAVENOUSLY 45 DROPS PER MINUTE FOR 1½ HOURS

Subject's Name	Before	During	Finish	1 hour later
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Wellman	10.8	15.3	16.8	11.2
Sister M.M.A.	10.3	15.7	16.3	10.1
Marquart	9.4	16.1	13.6	9.9
McTarnahan	9.4	15.5	9.9	8.2
Cleghorn	13.5	18.3	17.6	13.7

TABLE II. 11.0 MG. HISTAMINE DIPHOSPHATE IN 1000 C.C. NORMAL SALINE, INTRAVENOUSLY 45 DROPS PER MINUTE FOR 6 HOURS

Subject's Name	Before	2 hours	4 hours	6 hours Finish	2 hours later
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Wick	12.6	17.5	17.8	18.0	8.1
Taylor	10.6	16.9	18.2	19.1	8.4

TABLE III. .275 MG. HISTAMINE DIPHOSPHATE SUBCUTANEOUS INJECTION

Subject's Name	Before	1 hour after	2 hours	3 hours	4 hours
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Marquart	10.2	11.6	11.5	11.0	10.2
Sister M.M.A.	10.5	11.8	11.5	9.0	9.9
Wellman	10.4	11.5	12.6	11.0	10.6

TABLE IV. BY IONTOPHORESIS 10 C.C. OF A 1% SOL. OF HISTAMINE DIPHOSPHATE AT 6 MILLIAMPERES FOR 15 MINUTES*

Subject's Name	Before	During	After 15 minutes	After 1 hour	After 3 hours	After 4 hours
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Rod	11.7	18.2	18.7	15.5	12.2	11.4
Sister M.M.A.	10.6	17.8	15.5	14.2	11.0	10.2
Gill	9.6	19.8	13.2	9.4	9.2	9.6
Sauer	10.8	20.8	19.3	15.6	10.4	8.4
Morrison	8.9	15.2	14.7	11.2	9.2	8.6
Flannery	10.2	13.9	13.9	13.4	10.5	8.4

using the Van Slyke volumetric apparatus. The oxygen content of venous blood varies normally from 10 to 18 volumes per cent, arterial blood normally 15 to 23 volumes per cent.

It can be observed by Tables I and II that the oxygen content of the venous blood reaches the arterial level during the intravenous injection of histamine. This arterial level is maintained throughout the time of administration, but drops back to the venous level within a short time after the injection is stopped.

As shown by Table III, the oxygen content is increased by subcutaneous injection. This increase lasts longer, but at no time does the oxygen content of the venous blood reach the arterial level.

By iontophoresis Table IV shows that the oxygen content of venous blood is increased to about the same level as by intravenous injection. However, the effects appear to be maintained longer.

****Histamine diphosphate suspension in oil and wax supplied through the courtesy of Endo Products, Inc.

TABLE V. 30 MICROGRAMS B_{12} (RUBRAMIN) BY SUBCUTANEOUS INJECTION**

Subject's Name	Before	After 1 hour	After 2 hours	After 3 hours
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Larson	11.8	11.8	11.8	11.8
Cleghorn	11.2	11.0	11.2	11.2

TABLE VI. 30 MG. OF d-TUBOCURARINE IN OIL AND WAX DEEP INTRAMUSCULAR INJECTION***

Subject's Name	Before	After 1 hour	After 3 hours	After 6 hours	After 8 hours	After 24 hours
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Flannery	10.4	15.8	15.8	16.1	16.7	18.1
Cleghorn	13.5	13.5	13.9	15.3	16.1	20.9
Rod	11.8	12.5	13.0	14.2	14.0	12.4
Marquart	10.1	12.0	12.2	11.5	11.0	10.2
Sauer	11.0	11.0	11.0	11.8	14.0	12.8

TABLE VII. VERY SPASTIC QUADRIPLEGIA CASES
Large Daily Doses of d-Tubocurarine in Oil and Wax.
Blood Taken Twenty-four Hours after Last Dose

Subject's Name	Amount daily	Volume Per Cent
Hitchcock	15 mg.	11.5
Sauer	15 mg.	12.0
Cleghorn	22.5 mg.	15.6
Wood	22.5 mg.	14.2
Johnson	30.0 mg.	16.8
Sullivan	30.0 mg.	18.3

TABLE VIII. ½ C.C. OF A HISTAMINE DIPHOSPHATE OIL AND WAX SUSPENSION 2.75 MG. PER C.C. INJECTED DEEP INTRAMUSCULARLY****

Subject's	Before	After 6 hours	After 18 hours	After 24 hours	After 48 hours	After 72 hours	After 96 hours
	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent	Volume Per Cent
Smith	11.4	16.2	16.2	16.4	16.4	12.9	11.6
Knutson	10.2	14.8	13.6	12.7	12.4	11.2	10.6
Sister M.M.A.	10.6	16.0	18.3	18.7	15.6	15.0	11.2
Marquart	11.0	17.6	17.6	17.6	16.4	14.7	12.1

Table V indicates that the subcutaneous injection of B_{12} (Rubramin) does not increase the oxygen content of venous blood.

In Table VI it is easy to observe that d-Tubocurarine in oil and wax injected deep intramuscularly does increase the oxygen content of venous blood, and over a considerable period of time. This is probably because of the histamine-like effect of d-Tubocurarine. Table VII shows that the effect varies in different subjects but remains constant in relationship to the amount given. We believe the prolongation due to the repository menstruum in which the d-Tubocurarine was given.

. The observation led us to use histamine diphosphate as a suspension, 2.75 mg. per c.c. in a menstruum of 2 per cent white beeswax and oxy-

*Powdered histamine diphosphate supplied through the courtesy of the Abbott Research Laboratories.

**Rubramin, Vitamin B_{12} Concentrate, supplied through the courtesy of E. R. Squibb & Sons.

***d-Tubocurarine Chloride in oil and wax supplied through the courtesy of Abbott Research Laboratories.

cholesterol derivatives dissolved in peanut oil. Code and Varco[12,13] in 1940, later Greenblatt, Feldman and Linder[20] in 1949 reported the use of histamine in a retarding menstruum.

Table VIII indicates that when the suspension is given deep intramuscularly this results in an increase of the venous blood oxygen content up to ninety-six hours. In most cases the increase is to an arterial level for over forty-eight hours.

COMMENT

Brickner and Franklin[9,18] in 1947 stated that the basic notion in the therapy of multiple sclerosis "calls for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be enforced for twenty-four hours a day. A drug-free interval of even a few minutes would suffice for an attack." Repository histamine may fulfill these criteria of therapy.

The possibility of producing gastric ulcers by the use of repository histamine[32] must be considered. Code, Varco, Walpole, Wangensteen and Hay[12,13,22,41] did produce them in dogs and cats by using histamine in beeswax. However, the dose used to do this was many hundred times the size of any dose we use. On the other hand, they did not produce ulcers in monkeys even though these were given the same large doses that had been used on dogs and cats. Bernstein[6,7] reports the successful treatment of peptic ulcer in man by the repeated injections of histamine. In our use of histamine by all methods we have never had a case in which the gastric acidity was not controlled by the taking of food or alkalizing powders.

We have also used repository histamine on patients with asthma, migraine, urticaria, and angioneurotic edema. These patients suffered no unfavorable reactions. In these cases the histamine effects were the same as those produced by the other methods of its administration, except that the "histamine lift" appeared to last longer when the suspension was used.

During our series, we have treated 254 patients with multiple sclerosis by intravenous histamine injections. Of these 106 are now administering histamine to themselves at home by iontophoresis and twenty-four are receiving the histamine suspension at the clinic. Practically all patients have received d-Tubocurarine in oil and wax intramuscularly and many of them B_{12} (Rubramin) by subcutaneous injection.

SUMMARY AND CONCLUSIONS

The Van Slyke and Stadie methods of venous blood oxygen content increase determination apparently can be used as a gauge in measuring the pharmacological effects of histamine in reference to its mode of administration.

The allergy theory of multiple sclerosis etiology and therapy, does not conflict with or displace the therapy calling for the prevention of vasospasm and continued vasodilatation.

The deep intramuscular injection of a retarding histamine suspension appears to measure up to the criterion of continued vasodilatation.

Injection of repository histamine in the proper dose two or three times a week appears at present to be the proper time interval.

We are of the opinion that a repository histamine suspension may be used successfully wherever hyposensitization or continued vasodilatation is indicated, our Van Slyke oxygen content tests leading us to believe that the prolonged histamine-like action of d-Tubocurarine in a repository menstruum, as given to our patients with multiple sclerosis, has increased the effectiveness of their histamine therapy.

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DEPARTMENTAL COURSE AND RESEARCH FELLOWSHIPS IN PEDIATRIC ALLERGY

The Pediatric Department of New York Medical College announces a course in pediatric allergy to be held on Wednesdays, 10:00 A.M. to 4:00 P.M., October to March. The course, consisting of lectures and seminars, demonstrations of laboratory and clinical procedures, and animal experimentation, will be given by Dr. Bret Ratner and Pediatric Staff.

Two full-time fellowships in pediatric allergy, one starting July 1, the other January 1, are offered by New York Medical College. The fellowships, running from one to two years, consist of intensive training in immunology, animal research, and allergy. Information is obtainable from the office of the Dean.

HYPO-ALLERGIC PENICILLIN

S. WILLIAM SIMON, M.D., F.A.C.A.
Dayton, Ohio

THE problem of when to give and when to refrain from giving penicillin has been before the medical profession since the drug was introduced and the physician was cautioned as to sensitization and possible reactions. In seriously ill patients there is no problem as the recovery of the patient is tantamount and possible sensitization or reactions are not even considered. However, in some acutely ill patients, penicillin is withheld at times, while other less efficacious drugs are used, rather than to chance sensitization and possibly prevent the use of penicillin on some later occasion. In those with a history of past reactions from penicillin, the drug is either not given or, if so, with considerable trepidation even with so-called "desensitization." Most reactions are minor and in most instances can be ignored, but there is a small group of patients who react more severely, at times alarmingly, in whom discontinuance of the drug is essential.[19] In the latter, dangerous situations such as exfoliative dermatitis may result if penicillin sensitivity is not recognized promptly.[10,13,21]

The skin test, so ably described by Peck and his co-workers,[23] lacks reliability, as reactions have developed after negative immediate and delayed tests and none have followed the frequent positive tests.[2] In some patients, sensitivity seems to be transient, and subsequent courses of penicillin may be given without trouble; others develop an apparent permanent sensitivity.[21,23,26]

When penicillin acts as an antigen, either complete in itself or as a hapten in combination with human or bacterial protein,[30] the reactions have been divided into the following groups by Feldman[12]:

1. Allergic dermatitis of the contact type.
2. Drug and serum-like reactions.
3. Erythemato-vesicular reactions.
4. Tuberculin type reactions.
5. Arthus-like reactions.

All of these types, on repeated observations, may show wide variation in the degree of hyersensitivity to penicillin.[4,11] There is apparently no correlation between a past history of personal or familial allergies, previous skin disease, drug intolerance, previous penicillin therapy or reactions referable to it and the incidence of reaction.[15,25] Penicillin sensitivity has been found to exist in the absence of trichophytin sensitivity and may not exist in the presence of trichophytin sensitivity.[22]

Dr. Simon is Chief, Allergy Clinic, Brown General Hospital, Veterans Administration Center, Dayton, Ohio.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

"Decapryn" Succinate "Minergic" Solution was supplied through the courtesy of The Wm. S. Merrell Company, Cincinnati.

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The only reactions we have considered are the two most common ones. Urticaria usually appears five to fourteen days after stopping the drug. The erythemato-vesicular reactions which are id reactions, very much like dermatitis medicamentosa, involve primarily the groins, legs, hands and feet, occurring usually within twenty-four hours of starting the drug and subsiding in three to four days after its cessation.[2,15] Circulating antibodies have been demonstrated in the urticarial type but not in the erythemato-vesicular. The urticaria is the result of a mechanism analogous to that observed in the classic urticaria of serum allergy. The acute edematous swelling characteristic of the wheal is due to increased capillary permeability which follows the release of a histamine-like substance at the subpapillary level of the skin. The actual shock cells are probably located within the walls of the smaller vessels and capillaries in the corium.[2] A period of anergy generally follows for a week after cessation of symptoms.[31]

Rostenberg and Welch have proven that sensitization to penicillin may be produced in most persons by repeated injections.[24,25] The literature abounds with the per cent of skin reactions produced, varying from 1.2 to 20 per cent and averaging roughly 5 per cent to crystalline penicillin.[1,15,16,18,23,25,29] We offer no particular explanation for the 1.2 per cent given by Lepper and his associates, feeling that they were either very lucky, which is improbable, or that the patients were not followed for a long enough period to determine whether or not reactions from penicillin developed.

In the newer types of penicillin preparations, efforts have been made to impede the absorption so that blood levels are prolonged and the necessity of frequent injections removed. Penicillin in oil and beeswax[9] which frequently produced pain at the site of injection, and occasionally indurations and even sterile abscesses, has been supplanted in favor of procaine penicillin. While beeswax was an infrequent sensitizer, in adding procaine to the penicillin, we have added another potent antigen.[6] Penicillin blood levels with the latter are generally higher over a longer period than with the former and the procaine portion of the practically insoluble salt also gives a local anesthetic action.[18]

Caronamide has also been used to delay excretion of the penicillin and thereby prolong blood levels, but the consensus at present seems to be that the benefits achieved by raising the blood levels must be balanced against the dangers of administering sufficient caronamide to obtain this effect.[14,17]

The question of blood levels in relation to therapeutic response has caused a great deal of controversy. We know many ways of raising and prolonging the raised blood levels but we are not in agreement as to the efficacy of this maneuver. It has not been demonstrated that continuous blood levels of penicillin are necessary or desirable for the treatment of all infections and a considerable amount of experimental evidence has accumulated which casts doubt upon this. Primarily, measurement of the blood

penicillin level does not reliably indicate the concentration of penicillin in infected tissue.[3,5,27] It is not necessary to maintain the blood and tissue concentration of penicillin continuously at effective levels in order to attain cure. Paradoxically, greatly increased concentrations of penicillin appear to decrease the death rate of certain organisms rather than to increase it. Obviously, the clinical response of the patient is a more reliable index to adequate therapy than laboratory determinations.[7,8]

Therefore, we decided to use aqueous crystalline penicillin in this series, as its actions were limited rather than extended, no possible toxic substances or other antigens had been added, and we could make comparable blood level studies easier. However, to diminish or control the reactions we added to this penicillin an antihistamine dissolved in the diluent. Antihistamines have been found to be of value in treating penicillin reactions by competing with histamine for attachment to the cell receptors in the skin[28] so they should be of infinitely more value in preventing these reactions in the same way. We had found Decapryn (dimethylaminoethoxymethylbenzylpyridine) Succinate to be superior to other antihistamines in this treatment and therefore preferred to use it in prophylaxis. Many animal experiments had shown injected Decapryn to be completely absorbed and nontoxic.

Combinations of Decapryn Succinate with various pharmaceutical forms of penicillin were evaluated for their effect, or lack of effect on penicillin blood levels in rabbits. The dosage of penicillin administered to rabbits in these studies was 30,000 or 40,000 units per kilogram of body weight. This dosage is based on a report that the percentage of animals showing concentrations of penicillin in the serum in excess of 0.05 units per c.c. following such dosage will equal the per cent of patients showing concentrations of penicillin equal to, or greater than, 0.03 units per c.c. following the injections of 1 c.c. (300,000 or 400,000 units) of the same preparation. These studies[13] showed that Decapryn has little or no effect on the blood levels induced by various pharmaceutical forms of penicillin.

Diluent for the crystalline potassium penicillin G used consisted of normal saline to which was added Decapryn Succinate 5 mg. per c.c. The penicillin was uniform in that each c.c. contained 100,000 units of penicillin and 5 mg. of Decapryn Succinate dissolved in normal saline. Dosage was in varying amounts from 50,000 to 300,000 units or from 0.5 to 3.0 c.c. One patient received 1,000,000 units every three hours in 3 c.c. of Decapryn diluent (15 mg. Decapryn Succinate), night and day for fifteen days, without ill effect.

To have adequate controls, the entire hospital was divided into medical and surgical wards. All patients on the medical wards given aqueous crystalline penicillin were automatically given Decapryn-Penicillin while all patients on the surgical wards given aqueous penicillin received the same crystalline potassium penicillin G dissolved in normal saline but with nothing else added. The present figures deal with five months' experience, and

although more patients have been given penicillin and Decapryn-Penicillin than have been noted, only those reported patients are included.

Of 400 surgical patients on aqueous crystalline penicillin, twenty-six (6.5 per cent) developed skin reactions (Table I).

TABLE I

	No. of Patients	Penicillin Reactions	Per Cent of Reactions
Decapryn-Penicillin	292	7	2.4
Controls	400	26	6.5

Of 292 patients receiving Decapryn-Penicillin there were seven reactions (2.4 per cent). (The residents in the hospital who were charged with making the individual reports of the reactions to the regular penicillin and also to the Decapryn-Penicillin were definitely on the lookout for skin manifestations developing in patients on the combination. Probably no patient who developed even a semblance of a rash after receiving Decapryn-Penicillin was left unreported, where it is easily conceivable that many patients who were given the drug but developed no reactions were not reported. Therefore, it is believed that the actual percentage of reactions to Decapryn-Penicillin is much less than the 2.4 per cent noted.)

One patient was a sixty-two-year-old man with arteriosclerotic heart disease, aortic stenosis, ventricular fibrillation, pulmonary infarct and bronchopneumonia. He was receiving besides 150,000 units of Decapryn-Penicillin every six hours, Heparin, Dicumerol and Digitoxin. The generalized maculopapular confluent rash, which was most marked on the trunk, arose after two days of medication. It did not fade or change materially, although Decapryn-Penicillin was discontinued, in the remaining six days that he lived.

The second patient suffered from bilateral hydronephrosis, lobar pneumonia, uremia, and obstruction of the neck of the urinary bladder. Decapryn-Penicillin was given in doses of 100,000 units every eight hours for nine days and 200,000 units every eight hours for another two days. At this time he developed a generalized maculopapular rash which later coalesced. Decapryn-Penicillin was stopped, and the patient's eruption cleared rapidly on 25 mg. of Decapryn by mouth every four hours. Because it was felt that the excretion of penicillin was impeded by the kidney pathology and that in reality the penicillin blood levels were much higher than would be expected with the dose received, penicillin blood levels were run two days after penicillin was stopped. At this time the blood level was 15.5 micrograms per c.c. and the blood urea nitrogen was 185 mg. per cent.

The third patient received 50,000 units Decaphyn-Penicillin every four hours for two weeks in the treatment of chronic bronchiectasis. At the same time he was given aerosol penicillin. He developed generalized urticaria, migratory arthritis, and low grade fever, which cleared rapidly on

stopping all penicillin and administering Decapryn Solution by injection intramuscularly.

The fourth patient had pneumothorax with infection and was given Decapryn-Penicillin for eleven days in a dosage of 300,000 units twice daily. Urticaria developed on the eleventh day but cleared in one day on stopping penicillin and administering an antihistamine by mouth. Two days later Decapryn-Penicillin was again started and given without reaction.

The fifth patient was treated for lobar pneumonia with 100,000 units of Decapryn-Penicillin every eight hours for fourteen days, at which time he developed a mild urticaria with little pruritus. One day's treatment with oral antihistamines completely cleared the eruption. No further penicillin was given as it was not indicated.

The sixth patient who had a carcinoma of the left suprarenal area, possibly involving the kidney, received 300,000 units of Decapryn-Penicillin twice daily for five days. Eight days after the last dose generalized urticaria developed which cleared in two days without treatment.

The seventh patient had a very advanced Parkinson's disease, and in addition to 300,000 units of Decapryn-Penicillin every eight hours for fifteen days he was also receiving Artane orally. He had had hives at frequent intervals previously but none during the last five years. Generalized urticaria developed two weeks after the course of Decapryn-Penicillin was started.

Three luetics, all with histories of previous reactions to penicillin, were given 9,000,000 units of Decapryn-Penicillin each. Two of these had had urticaria and the other erythema multiforme previously when given penicillin, of such severity as to necessitate interrupting treatment. Two were given 300,000 units of Decapryn-Penicillin twice daily and the other 600,000 units of Decapryn-Penicillin once daily. All took the entire course without reaction and with good therapeutic response.

Five patients developed an erythemato-vesicular rash from regular crystalline penicillin. On stopping medication the rash cleared. When this same penicillin was again tried, rash reappeared. On changing to Decapryn-Penicillin, in the same dosage, the rash did not recur.

One patient received 200,000 units of Decapryn-Penicillin every six hours for four days. At the same time he was being given penicillin troches in the treatment of peptic ulcer. He developed a stomatitis, undoubtedly from the troches, but never any reaction from the injected Decapryn-Penicillin.

Another patient received crystalline penicillin in a dosage of 1,000,000 units every three hours for ten days, at which time he developed a punctate macular rash of the face and forehead. Because he was suffering from multiple liver abscesses it was deemed necessary to continue penicillin. Therefore, he was immediately switched to 1,000,000 units of penicillin dissolved in 3 c.c. of Decapryn diluent (15 mg. Decapryn) every three hours. This was continued for eighteen days. The rash cleared completely within

three days although the penicillin blood level was 12.8 micrograms per c.c. Good therapeutic effect was observed.

A patient who developed urticaria on regular crystalline penicillin was shifted to the same dose (100,000 units every eight hours) of Decapryn-Penicillin, and the urticaria cleared completely during the week he remained on this medication.

It can be seen that all patients who reacted to regular crystalline penicillin were not put on Decapryn-Penicillin as in the others they had had sufficient medication when the reaction occurred. Of the patients given Decapryn-Penicillin, 60 per cent had been given penicillin previously and 40 per cent were taking it for the first time. This information was not noted on the controls. Decapryn-Penicillin was given from one to eighty-two days and the average for all patients was 12.7 days (Table II). Dosage was from 100,000 to 8,000,000 units daily, with the average daily dose being 600,000 units and the average total dose for all patients being about 6,000,000 units. No changes were observed in the blood and urine examinations done before and after using Decapryn-Penicillin.

TABLE II. DECAPRYN-PENICILLIN

Duration of treatment	—1 to 82 days (average, 12.7 days)
24-hour dosage	—100,000 to 8,000,000 units (average, 600,000 units)
Total dosage	—200,000 to 40,000,000 units (average, 6,000,000 units)

When we first started using Decapryn-Penicillin, blood penicillin levels were performed on ten patients who were then on regular crystalline penicillin. These were checked against the levels twenty-four and forty-eight hours after shifting to Decapryn-Penicillin in the same dosage. Four were lower, two were higher and four were about the same. All were above detectable levels and therapeutic results were unchanged.

We were quite surprised to note detectable blood levels of penicillin after twenty-four hours when patients were given but one dose of 300,000 units of Decapryn-Penicillin.

Lately, in selected cases, we have been using Decapryn-Penicillin in oil which is crystalline potassium penicillin G 300,000 units, Decapryn (oil soluble—not the salt, succinate) 15 mg., and aluminum monostearate 2 per cent in each c.c. of sesame oil. This preparation was put up in 10 c.c. rubber-capped vials. Our results with Decapryn-Penicillin in oil have also been good in those penicillin-sensitive cases where it has been tried and thus far there have been no reactions in about forty patients. Penicillin blood levels have been about the same as with the same dosage schedule with Decapryn-Penicillin at one, four and eight hours and somewhat higher at twenty-four hours.

However, the advantage of Decapryn-Penicillin in oil over Decapryn-Penicillin is not in slowness of absorption but that it is stable in solution at room temperature, is always available and is more easily washed from a syringe than the old oil and beeswax preparations. Decapryn acts as an

excellent local anesthetic and either preparation may be injected into the deltoid muscle with no immediate or residual pain or tenderness. Patients shifted from regular aqueous crystalline penicillin to Decapryn-Penicillin have frequently remarked on the absence of pain and tenderness of the latter.

Work is in progress at present in treating many luetics with high dosage Decapryn-Penicillin in oil and this will be reported when completed. So far we have not attempted to use Decapryn-Penicillin intrathecally or in treating subacute bacterial endocarditis but this will be tried after suitable animal experiments.

DISCUSSION

For some years it has been known that antihistaminic drugs given orally at the time penicillin was being administered to patients with previous reactions would prevent some of these reactions from developing. We have gone one step further in preventing the development of penicillin reactions in many patients who, we believe, may have been sensitized to the drug.

Much argument might be forthcoming on the question of sustained high blood penicillin levels, but results lately seem at least as good with daily injections of sufficient aqueous crystalline penicillin. Procaine, another sensitizer, is not needed to delay absorption nor to act as a local anesthetic. However, it is possible that if the antihistaminic were added to procaine penicillin too it might prevent the development of reactions.

We have not attempted to measure therapeutic response with high level single dose crystalline penicillin versus Decapryn-Penicillin or Decapryn-Penicillin in oil, but the observations of others working with the Decapryn-Penicillin are that their results are at least as good as with the plain crystalline penicillin.

Side reactions to antihistamines given orally, which are extremely common, were not encountered in any of our patients. Penicillin and other drug reactions resulting in urticaria were treated by the use of intramuscular injections of 2 c.c. of the Decapryn diluent (10 mg. Decapryn Succinate) every three or four hours with better results than were obtained with any of the other common methods of treating this condition, including intravenous histamine.

It is a bit of arm chair philosophizing but the thought occurs that antihistaminics could be easily combined with other preparations which occasionally cause reactions and while possibly preventing these reactions, at the same time would make the injection of these remedies practically painless. To be considered are insulin, liver extract, vitamin B complex, thiamine chloride, et cetera.

SUMMARY

A new method of decreasing the number of penicillin reactions by the addition of an antihistamine (Decapryn) to the diluent is presented. In the

control group of 400 the percentage of reactions was 6.5, whereas in the group of 292 patients receiving Decapryn-Penicillin the percentage of reactions was only 2.4, which is a reduction in reactions of 63.1 per cent. The combination was practically painless on injection and the therapeutic results obtained were at least as good as with any other penicillin preparation now in use.

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(Continued on Page 289)

A WEEKLY MOLD SURVEY OF AIR AND DUST IN LEXINGTON, KENTUCKY

M. ELIZABETH WALLACE, R. H. WEAVER and M. SCHERAGO
Lexington, Kentucky

NEWTON, Scherago and Weaver (1948), in a study of the distribution of molds in outdoor air, indoor air, and house dusts in Kentucky, found differences in the mold flora of the different regions of the State which they studied. They also found differences in the mold content of the outdoor air, indoor air and house dusts. The extensiveness of their survey limited the number of samples that could be examined from any one locality. The present study was undertaken to study further the distribution of molds in outdoor air, indoor air and house dusts, using a single region (Lexington, Ky.) for the collection of a larger number of samples. Also, since both Sabouraud's agar and potato-glucose agar have been used recently in mold studies, the comparative values of the two media for the primary isolation of molds have been investigated.

MATERIALS AND METHODS

Modified Sabouraud's agar (Newton et al, 1948) and Bacto-potato-glucose agar were prepared with the pH adjusted to 3.0. One poured Petri plate of each medium was exposed for fifteen minutes to the outdoor air at the Kentucky Agricultural Experiment Station Farm and on Main Street, and to the indoor air at the Kentucky Theater, a residence in the southwestern section of the city, and a residence in the southeastern section of the city. Dust samples were also collected at the three indoor locations.

Exposures were made every seven days from July 20 through August 31. Then the residence in the southeastern section of the city had to be dropped from the survey list, and exposures at the remaining four locations were continued through September and October. A second brief survey was made at all of the original locations during the month of January. Exposures were made on January 4, 11, and 18.

After exposure the plates were incubated at room temperature until the colonies reached maturity. Then, the colonies of each of the macroscopically similar types of mold were counted and a representative of each type was subcultured on potato-glucose agar. The dusts were streaked out on plates of both Sabouraud's medium and potato-glucose agar, and subsequent procedures were the same as for the exposed plates.

Moist chamber cultures on potato-glucose agar adjusted to pH 5.6, were used for the microscopical identification of the molds.

A Manual of Soil Fungi (Gilman, 1945) was the chief reference used for the identification of the molds. Other references used were *The Asper-*

From the Department of Bacteriology, University of Kentucky.
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Dr. Scherago is an Associate Member of The American College of Allergists.

TABLE I. NUMBER AND DISTRIBUTION OF MOLD COLONIES

MOLD	KENTUCKY AGRICULTURAL EXPERIMENTAL STATION FARM															
	Outdoor Air															
	July		August					Sept.				Oct.				Total
	20	27	3	10	17	24	31	7	14	21	28	5	12	19	26	
Alternaria Geophilia		2	6	5	5	4	6	3	4	1	1	6	2	4	1	50
Aspergillus																
Fumigatus	2		2	2	2		2	2	1	2	3	4	1	4	2	29
Luchuensis	2	2	7	7	9	6	9	7	5	2	3	7	4	4	2	76
Niger	6	2	4	8	10	14	12	9	9	2	2	9	7	8	2	104
Versicolor			3	1		1		1	1	2	2	2	1	2		16
Spp.	1		2	2	2	1	1		1	1	2	2	1	3	1	20
Monilia Geophilia																0
Mucor Piriformis																0
Oospora Variabilis	4	1	1		2	2		1				1		1		13
Penicillium																
Albicans	1	1														2
Citrinum	49	47	56	47	52	45	48	39	35	43	46	55	46	49	47	704
Frequentans	7	7	9	15	17	10	20	14	13	6	8	10	14	7	7	164
Spp.	1	2	2	3	2	2	1	1	1	1	3	2	1	2	1	25
Stemphylium Piriforme	5	5	11	12	12	10	15	10	8	5	6	12	11	9	5	136
Sterile Hyphae					2										1	3
Unidentified																0
Totals	78	69	103	102	115	95	114	87	78	65	76	110	88	93	69	1342

MOLD	MAIN STREET															
	Outdoor Air															
	July		August					Sept.				Oct.				Total
	20	27	3	10	17	24	31	7	14	21	28	5	12	19	26	
Alternaria Geophilia	9	10	6	5	10	8	6	2	2	10	11	6	9	11	10	115
Aspergillus																
Fumigatus																0
Luchuensis																
Niger	15	17	18	17	21	17	19	15	12	16	18	18	18	17	19	257
Versicolor																0
Spp.																0
Monilia Geophilia																0
Mucor Piriformis																0
Oospora Variabilis							7	1								8
Penicillium																
Albicans																0
Citrinum	13	14	17	15	14	15	14	16	11	13	15	17	16	15	17	221
Frequentans	10	12	11	11	14	11	9	7	2	14	13	13	12	14	14	167
Spp.										11	12	8	6	12	12	61
Stemphylium Piriforme	3	3	5			4	3	1	2	4	4	4	4		4	41
Sterile Hyphae	12	11	9	8	11	9	4									64
Unidentified																0
Totals	62	67	66	56	70	64	62	42	29	68	73	66	65	69	76	934

MOLD	MOVIE THEATER																									
	Indoor Air																Dust									
	July		August					Sept.				Oct.				Total	July		August					Sept.		
	20	27	3	10	17	24	31	7	14	21	28	5	12	19	26		20	27	3	10	17	24	31	7	14	21
Alternaria Geophilia																0	12	9	10	12	11	9	17	9	11	9
Aspergillus																										
Fumigatus	1	3	2	3	1	1	2	2	2	2	2	2	1	1	2	27	16	15	10	15	16	14	14	10	14	14
Luchuensis	1	1	1	2			1	1		1		1	1	1	1	12	5	6	6	6	6	6	6	6	6	6
Niger																0										
Versicolor																0										
Spp.							1	1							1	3										
Monilia Geophilia																0										
Mucor Piriformis																0										
Oospora Variabilis	2				1		1		1				1			6										
Penicillium																										
Albicans																0										
Citrinum	2	3	2	1	2	1	3	3	1	2	3	2	2	1	3	31	17	15	13	17	16	15	17	13	16	15
Frequentans																0										
Spp.																0	6	5	6	7	7	8	7	6	7	9
Stemphylium Piriforme																0										
Sterile Hyphae																0										
Unidentified										1						1										
Totals	6	7	5	6	4	2	8	7	4	6	5	5	5	3	7	80	56	50	45	57	56	52	61	44	54	53

TABLE II. NUMBER AND DISTRIBUTION OF MOLD COLONI

Alternaria Geophilia		2	3	5	2	2	4	2	2	1	1	4	4	2	1	35
Aspergillus																
Fumigatus	1	2	1	2	2	1	1	2	1	2	2	1	2	2	2	24
Luchuensis			6	5	2	5	4	6	3	2	2	6	4	2	2	49
Niger		3	2	10	7	11	8	6	8	2	1	6	5	5	3	77
Versicolor	2		2	1		2	1	1	1		1	1	1	1		14
Spp.		1	1	2	1	1	2	1	2			1	2	1	1	16
Monilia Geophilia	1															1
Mucor Piriformis																0
Oospora Variabilis	3	1	1	1	1	2							1			10
Penicillium																
Albicans		1														1
Citrinum	21	29	28	39	47	40	41	34	29	21	30	39	38	31	29	486
Frequentans	9	9	5	11	15	8	17	12	12	9	11	9	10	11	9	157
Spp.	2	3	2	4	1	1	3	2	1	1	1	1	1	1	2	26
Stemphylium Piriforme	1	6	4	6	13	6	12	6	6	4	5	7	9	4	6	95
Sterile Hyphae					1					1						2
Unidentified																0
Totals	40	57	55	86	92	79	93	72	65	43	54	75	77	60	55	993

Alternaria Geophilia	11	7	4	7	8	5	6	1	2	9	13	5	8	10	2	98
Aspergillus																
Fumigatus																0
Luchuensis																0
Niger	14	11	12	13	17	13	18	9	10	15	14	13	15	14	13	201
Versicolor																0
Spp.																0
Monilia Geophilia																0
Mucor Piriformis																0
Oospora Variabilis							1									1
Penicillium																
Albicans																0
Citrinum	12	13	14	14	19	10	10	13	10	12	12	12	14	15	11	191
Frequentans	11	8	8	8	12	9	7	5	1	12	9	9	9	13	8	129
Spp.										13		7	5	13	7	45
Stemphylium Piriforme		2	3	2		2	1	1	1			4			1	17
Sterile Hyphae			6		8	6	1	1								22
Unidentified									1							1
Totals	48	41	47	44	64	45	44	30	25	61	48	50	51	65	42	705

Alternaria Geophilia																0	11	8	7	12	11	9	11	6	11	8
Aspergillus																										
Fumigatus	1	1	1	1	1	1	2	1		1	3	1	1	1	1	17	12	10	8	13	12	10	13	8	12	10
Luchuensis	1	1			1	1	1	1	2	1	1	1	1	1	1	14	4	3	5	4	3	4	4	4	3	4
Niger																0										
Versicolor																0										
Spp.			2				1									3										
Monilia Geophilia																0										
Mucor Piriformis																0										
Oospora Variabilis	1	1		1	1		2		2		1	1	1			11										
Penicillium																										
Albicans																0										
Citrinum	1	4	1	1	2	1	1	1	1	2	2	1	1	1	2	22	15	12	10	15	14	12	15	10	14	12
Frequentans																0										
Spp.																0	4	1	2	2	2	4	1	2	3	2
Stemphylium Piriforme																0										
Sterile Hyphae																0										
Unidentified																0										
Totals	4	7	4	3	5	3	7	3	5	4	7	4	4	3	4	67	46	34	32	46	42	39	44	30	43	36

COLONIES UPON POTATO GLUCOSE AGAR DURING THE SUMMER MONTHS

Dust											
		Sept.				Oct.				Total	Total
4	31	7	14	21	28	5	12	19	26		Air & Dust
9	17	9	11	9	10	11	9	9	10	158	158
4	14	10	14	14	14	14	10	13	14	203	230
6	6	6	6	6	6	6	6	5	7	89	101
										0	0
										0	0
										0	3
										0	0
										0	0
										0	6
										0	0
5	17	13	16	15	15	16	11	16	15	227	258
										0	0
8	7	6	7	9	7	8	9	4	5	101	101
										0	0
										0	0
										0	1
2	61	44	54	53	52	55	45	47	51	778	858

RESIDENCE, SOUTHWESTERN SECTION OF CITY

Indoor Air															
July		August					Sept.				Oct.				Total
20	27	3	10	17	24	31	7	14	21	28	5	12	19	26	
															0
															0
															0
5	2	2	7	3	7	3	5	4	4	3	3	4	2	2	56
															0
	1		2		1				1		1				6
															0
1	1	1	3	2	3	2	4	6	2	3	2	3	1	2	36
1	1	1	2	1	2	1	2	1	1			3	1	1	18
															0
5	4	8	10	10	14	17	14	7	6	5	5	11	6	4	126
3	5	7	9	13	18	21	12	8	5	6	6	10	8	5	136
1	2	1	2	4	2	2		2	1	2	4	3	5	1	32
															0
			1		1						1				3
			1									2			3
16	16	20	37	33	48	46	37	28	20	19	22	36	23	15	416

Dust																
July		August					Sept.				Oct.				Total	Total
20	27	3	10	17	24	31	7	14	21	28	5	12	19	26		Air & Dust
7	4	5	6	8	5	7	5	5	7	6	5	5	5	4	84	84
															0	0
8	6	7	8	8	6	8	7	6	8	8	7	8	8	5	108	108
															0	56
															0	0
5	3	4	5	5	4	9	4	4	5	5	4	3	4	3	67	73
															0	0
															0	36
															0	18
															0	0
10	9	8	10	11	9	10	8	9	12	12	10	12	9	8	147	273
10	8	8	9	10	8	9	8	8	10	9	8	8	8	7	128	264
8	1	6	7	6	4	9	7	6	6	4	5	3	3	3	78	110
															0	0
															0	3
															0	3
48	31	38	45	48	36	52	39	38	48	44	39	39	37	30	612	1028

RESIDENCE, SOUTHEASTERN SECTION OF CITY

Indoor Air								Dust								
July		August					Total	July		August					Total	Total
20	27	3	10	17	24	31		20	27	3	10	17	24	31		Air & Dust
							0								0	0
							0								0	0
							0	4	5	5	4	8	4	4	34	34
							0								0	0
2	2	3	1	1	2	3	14	8	8	6	7	9	5	7	50	64
							0								0	0
							0								0	0
4	5	7	7	8	15	9	55								0	55
2	3	4	2	4	3	1	19								0	19
							0								0	0
15	12	15	13	18	20	11	104	9	8	8	9	10	6	9	59	163
							0								0	0
		1	1	1		2	5	3	3	3	3	8	6	3	29	34
							0								0	0
							0								0	0
							0								0	0
23	22	30	24	32	40	26	197	24	24	22	23	35	21	23	172	369

LD COLONIES UPON SABOURAUD'S AGAR DURING THE SUMMER MONTHS

9	11	6	11	8	8	11	6	8	8	135	135
0	13	8	12	10	10	12	8	10	10	158	175
4	4	4	3	4	3	4	3	2	5	55	69
										0	0
										0	0
										0	3
										0	0
										0	0
										0	11
										0	0
2	15	10	14	12	12	15	10	12	12	190	212
										0	0
4	1	2	3	2	1	2	4	1	2	33	33
										0	0
										0	0
										0	0
9	44	30	43	36	34	44	31	33	37	571	638

															0
															0
															0
1	2	2	5	2	4	2	4	2	1	2	3	4	2	2	38
															0
	1		1		2				1		1			1	7
															0
1	1	1	1	2	1	1	2		1	1	2	1	2	2	19
1	1	2	2	1	3	1		1			1	1	1	1	16
															0
2	2	5	6	6	13	16	14	9	2	3	3	7	4	3	95
2	3	4	7	10	16	17	9	5	3	4	5	8	4	2	99
2	2	1	1	1	1	2		1	1	1	4	3	2		22
															0
		1	1				2								4
												1			1
9	12	16	24	22	40	39	31	18	9	11	19	25	15	11	301

3	1	3	4	4	3	5	5	4	4	5	2	2	2	2	49	49
															0	0
6	3	5	7	6	5	6	7	5	6	5	3	4	3	3	74	74
															0	38
															0	0
1	1	2	1	3	2	5	4	3	2	4	1	1	2	1	33	40
															0	0
															0	19
															0	16
															0	0
8	7	6	8	9	7	8	8	7	9	8	7	9	7	5	113	208
6	5	5	6	7	7	8	8	7	7	6	5	6	5	5	93	192
2		1	1	2	2	5	7	2	3	1	1	1	1	1	30	52
															0	0
															0	4
															0	1
26	17	22	27	31	26	37	39	28	31	29	19	23	20	17	392	693

							0								0	0
							0								0	0
							0	3	2	3	3	4	1	2	18	18
							0								0	0
2	1	2	1	2	1	2	11	7	5	6	6	7	3	6	40	51
						2	2								0	2
							0								0	0
2	4	5	6	6	11	5	39								0	39
1	2	3	1	1	1	1	10								0	10
							0								0	0
6	9	11	8	13	19	9	75	7	6	7	7	8	4	7	46	121
							0								0	0
		1		1	1	2	5	2	1	2	2	3	2	1	13	18
							0								0	0
							0								0	0
							0								0	0
11	16	22	16	23	33	21	142	19	14	18	18	22	10	16	117	259

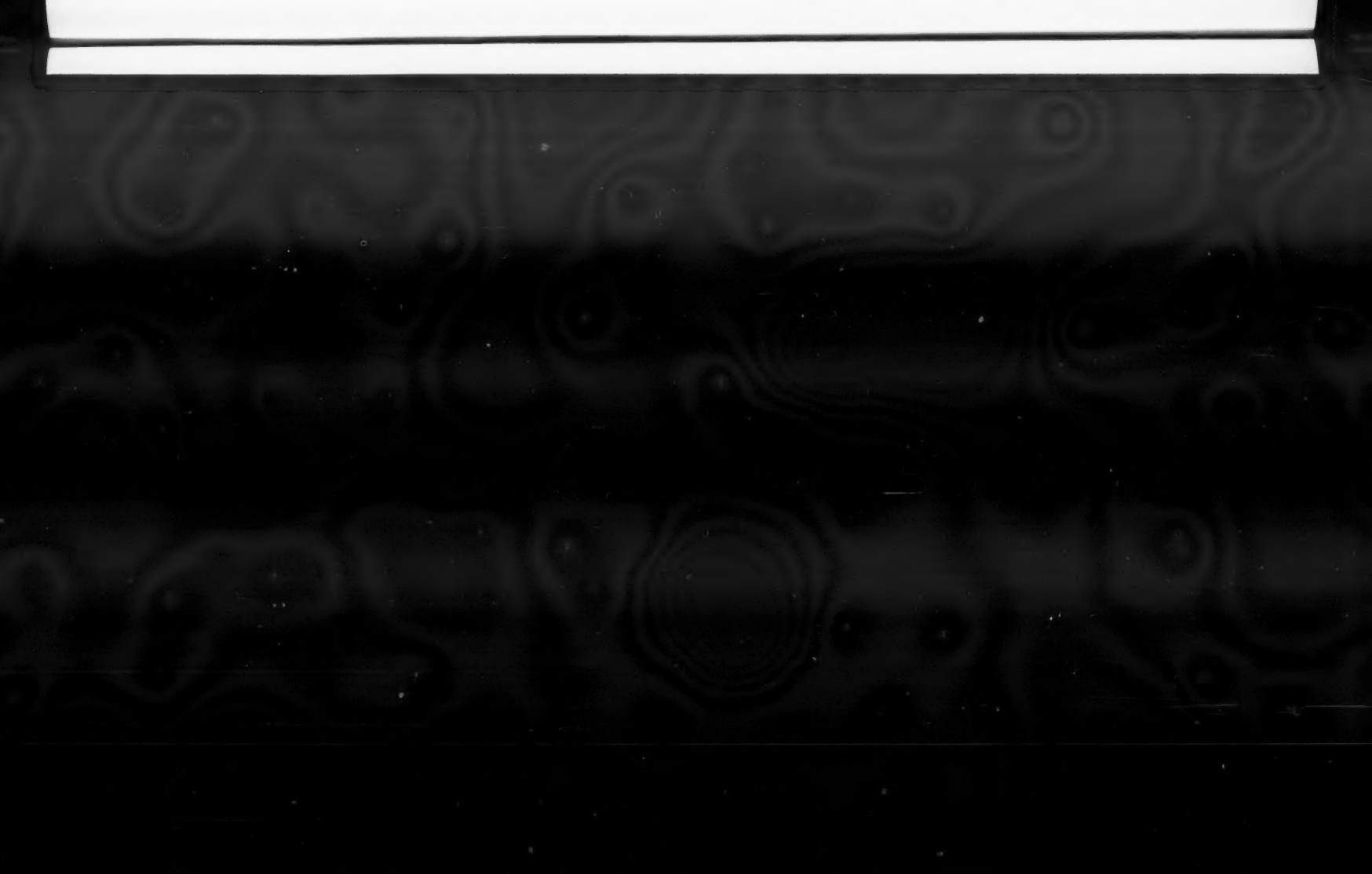


TABLE III. NUMBER OF COLONIES OF MOLDS FOUND DURING THE SUMMER MONTHS

Mold	Potato Glucose Agar								Sabouraud's Agar							
	1*	2	3		4		5		1*	2	3		4		5	
			A	B	A	B	A	B			A	B	A	B	A	B
Alternaria	50	115	0	158	0	84	0	0	35	98	0	135	0	49	0	0
Aspergillus	245	257	42	392	62	175	14	84	180	201	34	213	45	107	13	58
Monilia	0	0	0	0	0	0	55	0	1	0	0	0	0	0	0	0
Mucor	0	0	0	0	36	0	19	0	0	0	0	0	19	0	39	0
Oospora	13	8	6	0	18	0	0	0	10	1	11	0	16	0	10	0
Penicillium	895	449	31	328	294	353	109	88	670	365	22	223	216	236	80	59
Stemphylium	136	41	0	0	0	0	0	0	95	17	0	0	0	0	0	0
Sterile hyphae	3	64	0	0	3	0	0	0	2	22	0	0	4	0	0	0
Unidentified	0	0	1	0	3	0	0	0	0	1	0	0	1	0	0	0

*1 = Ky. Agr. Exp. Sta. Farm, Outdoor Air.
2 = Main Street, Outdoor Air.
3 = Ky. Theater.
4 = Residence, SW section city.
5 = Residence, SE section city.

A = Indoor air.
B = House dust.

TABLE IV. PRODUCTIVITY OF SABOURAUD'S AGAR AND POTATO-GLUCOSE AGAR FOR GENERA OF MOLDS FOUND IN THE OUTDOOR AIR, INDOOR AIR AND HOUSE DUSTS DURING THE SUMMER MONTHS

Mold	Outdoor Air		Indoor Air		Dusts	
	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar
Alternaria	7.82%	7.24%	0.00%	0.00%	17.02%	15.49%
Aspergillus	22.40	22.03	18.03	17.04	34.97	35.26
Monilia	0.05	0.00	0.00	0.00	0.00	0.00
Mucor	0.00	0.00	11.36	13.13	0.00	0.00
Oospora	0.64	0.92	7.25	6.20	0.00	0.00
Penicillium	60.74	58.99	62.32	62.62	47.92	49.22
Stemphylium	6.58	7.77	0.00	0.00	0.00	0.00
Sterile hyphae	1.41	2.94	0.78	0.43	0.00	0.00
Unidentified	0.05	0.00	0.19	0.57	0.00	0.00
	99.69%	99.89%	99.93%	99.99%	99.91%	99.97%

gilli (Thom and Church, 1926), *A Manual of the Aspergilli* (Thom and Raper, 1945), and *The Penicillia* (Thom, 1930).

RESULTS

The results of the summer survey with potato-glucose agar are shown in Table I and with Sabouraud's medium in Table II. As can be seen from these two tables, the following molds were isolated and identified: *Alternaria geophilia, Aspergillus fumigatus, Aspergillus luchuensis, Aspergillus niger, Aspergillus versicolor, Aspergillus* spp., *Monilia geophilia, Mucor piriformis, Oospora variabilis, Penicillium albicans, Penicillium citrinum, Penicillium frequentans, Penicillium* spp., and *Stemphylium piriforme.* With both media *Penicillium citrinum, Aspergillus niger* and *Aspergillus fumigatus* were the most numerous and most widely distributed species.

The number of colonies of each genus of mold that were isolated from all five sources is shown in Table III. As can be seen from this table, the Station Farm consistently yielded the highest plate counts and the

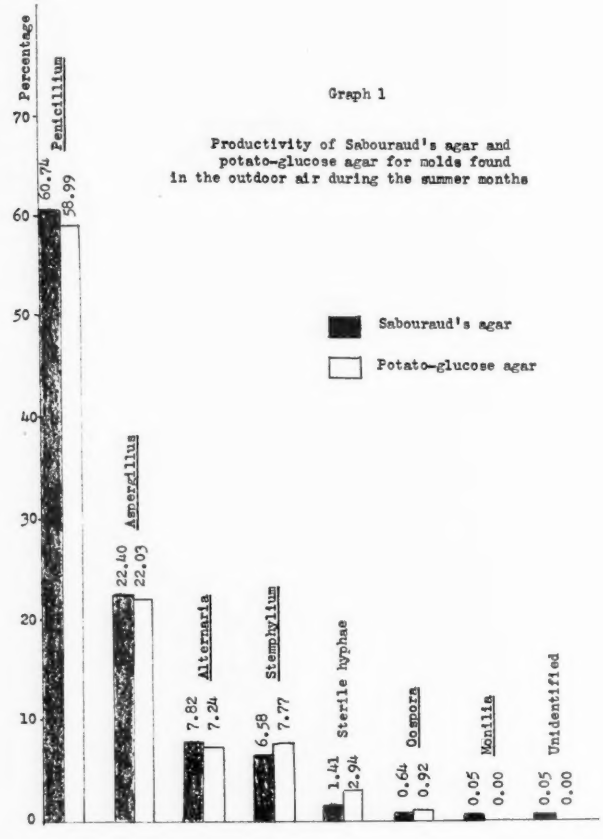
TABLE V. NUMBER AND DISTRIBUTION OF MOLD COLONIES UPON POTATO GLUCOSE AGAR DURING THE WINTER

NAME OF MOLD	KY. AGR. EXP. STA. FARM				MAIN STREET				MOVIE THEATER									RESIDENCE, SOUTHWESTERN SECTION CITY									RESIDENCE, SOUTHEASTERN SECTION CITY								
	Outdoor Air				Outdoor Air				Indoor Air				Dust				Total Air and Dust	Indoor Air				Dust				Total Air and Dust	Indoor Air				Dust				Total Air and Dust
	Jan.				Jan.				Jan.				Jan.					Jan.				Jan.					Jan.				Jan.				
	4	11	18	Total	4	11	18	Total	4	11	18	Total	4	11	18	Total		4	11	18	Total	4	11	18	Total		4	11	18	Total	4	11	18	Total	
Alternaria																																		
Geophilia				0	3	3		6				0	12	11	9	32	32				0				0	0				0				0	0
Spp.				0				0				0				0	0				0		4	4	4	12				0				0	0
Asperqillus																																		
Fumigatus				0				0	3	1	2	6	16	14	10	40	46				0				0	0				0				0	0
Luchuensis				0				0	2			2	5	7	5	17	19				0	5	5	5	15	15				0	5	2	4	11	11
Niger	3	5	4	12	9	11	8	28				0				0	0	1	1	2	4				0	4				0				0	0
Versicolor				0				0				0				0	0				0				0	0	9	9	7	25	8	4	7	19	44
Spp.				0				0				0				0	0				0	3	3	3	9	9				0				0	0
Mucor																																		
Piriformis				0				0				0				0	0			1	1				0	1	7	9	5	21				0	21
Penicillium																																		
Citrinum	15	18	14	47	7	10	5	22	3	3	2	8	17	16	17	50	58	4	3	5	12	8	8	9	25	37	10	11	8	29	8	7	8	23	52
Frequentans	8	9	8	25	6	9	5	20				0				0	0	3	1	4	8	7	8	8	23	31				0				0	0
Spp.	1		1	2				0				0	6	9	7	22	22	1	1	1	3				0	3	6	7	3	16	2	1	3	6	22
Stemphylium																																		
Piriforme	2	4	3	9				0				0				0	0				0				0	0				0				0	0
Total	29	36	30	95	25	33	18	76	8	4	4	16	56	57	48	161	177	9	6	13	28	27	28	29	84	112	32	33	23	91	23	14	22	59	159

TABLE VI. NUMBER AND DISTRIBUTION OF MOLD COLONIES UPON SABOURAUD'S AGAR DURING THE WINTER

NAME OF MOLD	KY. AGR. EXP. STA. FARM				MAIN STREET				MOVIE THEATER									RESIDENCE, SOUTHWESTERN SECTION CITY									RESIDENCE, SOUTHEASTERN SECTION CITY								
	Outdoor Air				Outdoor Air				Indoor Air				Dust				Total Air and Dust	Indoor Air				Dust				Total Air and Dust	Indoor Air				Dust				Total Air and Dust
	Jan.				Jan.				Jan.				Jan.					Jan.				Jan.					Jan.				Jan.				
	4	11	18	Total	4	11	18	Total	4	11	18	Total	4	11	18	Total		4	11	18	Total	4	11	18	Total		4	11	18	Total	4	11	18	T otal	
*Alternaria																																		
Geophilia				0	1			1				0	10	8	6	24	24				0				0	0				0				0	0
Spp.				0				0				0				0	0				0	1	2	2	5	5				0				0	0
Asphergillus																																		
Fumigatus				0				0	1	2	2	5	13	12	8	33	38				0				0	0				0				0	0
Luchuensis				0				0				0	3	5	3	11	11				0	2	2	2	6	6				0	3	1	1	5	5
Niger	2	4	3	9	6	9	7	22				0				0	0	2	2	1	5				0	5				0				0	0
Versicolor				0				0				0				0	0				0				0	0	6	8	3	17	5	4	3	12	29
Spp.				0				0				0				0	0				0	1	1	1	3	3				0				0	0
Mucor																																		
Piriformis				0				0				0				0	0	1			1				0	1	4	7	1	12				0	12
Penicillium																																		
Citrinum	11	13	11	35	6	7	6	19	1	2	1	4	13	15	17	45	49	3	2	3	8	5	5	7	17	25	8	9	5	22	6	6	7	19	41
Frequentans	7	10	8	25	6	4	4	14				0				0	0	3	2	2	7	3	3	3	9	16				0				0	0
Spp.			2	2				0				0	1	3	3	7	7		1	1	2				0	2	1	4	1	6	2	1	1	4	10
Stemphylium																																		
Piriforme	2	4	2	8				0				0				0	0				0				0	0				0				0	0
Total	22	31	26	79	19	20	17	56	2	4	3	9	40	43	37	120	129	9	7	7	23	12	13	15	40	63	19	28	10	57	16	12	12	40	97

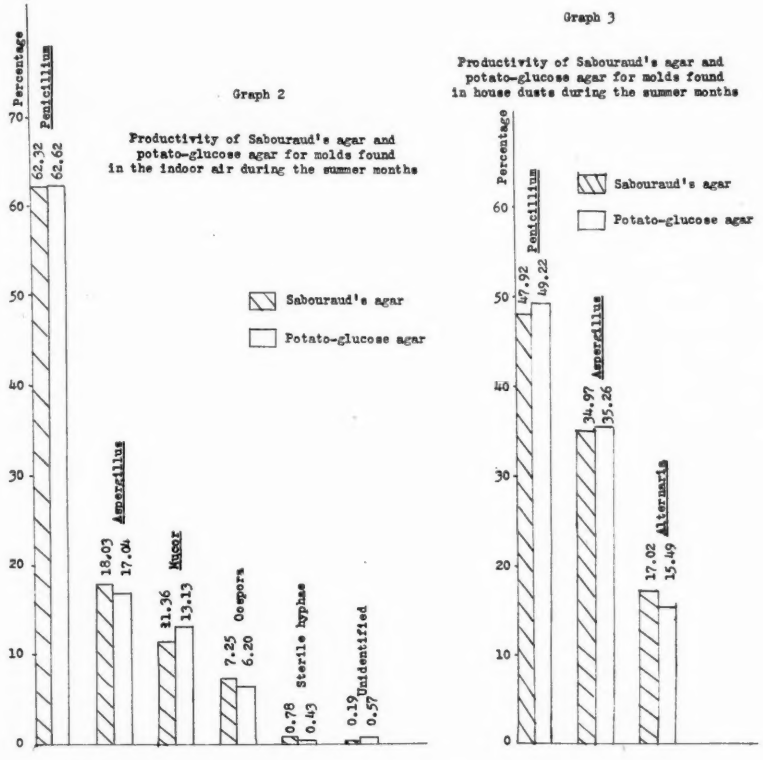
greatest diversity of species. This might have been due to the fact that the exposures were made near a barn in which cattle were housed; therefore, there was probably more dust in the air than at the other locations. The plate counts of the air in the Kentucky Theater were very low, but the



dust counts were relatively high. A possible explanation for the low "air" counts is the powerful air washing system that was in continuous operation at the theater.

Table III also shows that *Alternaria* was found in moderately large numbers in the outdoor air from both locations and in the dusts from the theater and the southwest residence although it was not found in the indoor air from the same locations nor in the dust or the indoor air from the southeast residence. *Aspergillus* was more prevalent in the dusts than in the indoor or the outdoor air. *Mucor* was present exclusively in the

indoor air. *Monilia* was found in significant numbers only in the indoor air from the southeast residence. *Oospora* was more abundant in the indoor than in the outdoor air and was not found in the dusts. *Penicillium* was present in high percentages in all three sources from all the locations.



Stemphylium was found exclusively in the outdoor air. A glance at Tables I and II will show that there was no appreciable variation in the species within the various genera of molds that were present in the indoor air, the outdoor air, and the dusts.

The difference in the productivities of the two media, as revealed in Tables III and IV and Graphs 1, 2, and 3, was apparently more quantitative than qualitative. There was generally a higher count of each mold on potato-glucose agar than on Sabouraud's agar, but there was no difference in the types that occurred, nor in the relative frequency of occurrence.

The results of the January survey are shown in Tables V, and VI; those with potato-glucose agar in Table V, and those with Sabouraud's agar in Table VI. From these two tables it can be seen that the following molds were isolated and identified: *Alternaria geophilia, Alternaria* spp.,

TABLE VII. NUMBER OF COLONIES OF MOLDS FOUND DURING THE WINTER

Mold	Potato-Glucose Agar								Sabouraud's Agar							
	1*	2	3		4		5		1*	2	3		4		5	
			A	B	A	B	A	B			A	B	A	B	A	B
Alternaria	0	6	0	32	0	12	0	0	0	1	0	24	0	5	0	0
Aspergillus	12	28	8	57	4	24	25	30	9	22	5	44	5	9	17	17
Monilia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mucor	0	0	0	0	1	0	21	0	0	0	0	0	1	0	12	0
Oospora	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Penicillium	94	42	8	72	23	48	45	29	62	33	4	52	17	26	28	23
Stemphylium	9	0	0	0	0	0	0	0	8	0	0	0	0	0	0	0
Sterile hyphae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unidentified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*1—Ky. Agr. Exp. Sta. Farm, Outdoor Air.
2—Main Street, Outdoor Air.
3—Ky. Theater.
4—Residence, SW section city.
5—Residence, SE section city.
A—Indoor air.
B—House dust.

TABLE VIII. PRODUCTIVITY OF SABOURAUD'S AGAR AND POTATO-GLUCOSE AGAR FOR GENERA OF MOLDS FOUND IN THE OUTDOOR AIR, INDOOR AIR AND HOUSE DUSTS DURING THE WINTER

Mold	Outdoor Air		Indoor Air		Dusts	
	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar	Sabouraud's Agar	Potato-Glucose Agar
Alternaria	0.75%	3.50%	0.00%	0.00%	14.50%	14.30%
Aspergillus	23.16	23.36	30.22	27.64	35.00	36.66
Monilia	0.00	0.00	0.00	0.00	0.00	0.00
Mucor	0.00	0.00	14.60	16.43	0.00	0.00
Oospora	0.00	0.00	0.00	0.00	0.00	0.00
Penicillium	70.97	67.74	55.03	56.77	50.50	48.43
Stemphylium	5.08	5.26	0.00	0.00	0.00	0.00
Sterile hyphae	0.00	0.00	0.00	0.00	0.00	0.00
Unidentified	0.00	0.00	0.00	0.00	0.00	0.00
	99.96%	99.86%	99.85%	99.84%	100.00%	99.39%

Aspergillus fumigatus, Aspergillus luchuensis, Aspergillus niger, Aspergillus versicolor, Aspergillus spp., *Mucor piriformis, Penicillium citrinum, Penicillium frequentans, Penicillium* spp., and *Stemphylium piriforme. Penicillium citrinum, Aspergillus niger,* and *Aspergillus fumigatus* were again the most numerous and most widely distributed species.

In Table VII are shown the numbers of each genus of mold isolated from each of the five sources during January on potato-glucose agar and Sabouraud's agar. In this table it can be seen that, as in the summer survey, the highest plate counts were obtained on the Experiment Station Farm. Again, the counts from the air in the Kentucky Theater were low and the dust counts were high.

The counts from the air during the January survey were lower than during the summer, but the dust counts were similar. No *Alternaria* were found in the outdoor air on the Station Farm and much less on Main Street than during the summer although it was equally prevalent in the dusts from the theater and the southwest residence. Also, no *Oospora, Monilia* nor *Penicillium albicans,* was found in the January survey. Other-

TABLE IX. SUMMER/WINTER COLONY COUNTS OF MOLD GENERA FOUND ON POTATO-GLUCOSE AGAR AND SABOURAUD'S AGAR FROM OUTDOOR AIR, INDOOR AIR AND HOUSE DUSTS*

Mold	Potato-Glucose Agar			Sabouraud's Agar			Totals			
	Outdoor Air	Indoor Air	House Dusts	Outdoor Air	Indoor Air	House Dusts	Outdoor Air	Indoor Air	House Dusts	Total
Alternaria	165/6	0/0	242/44	133/1	0/0	184/29	298/7	0/0	426/73	724/80
Aspergillus	502/40	118/37	551/111	381/31	92/27	378/70	883/71	210/64	929/181	2022/316
Monilia	0/0	0/0	0/0	1/0	0/0	0/0	1/0	0/0	0/0	1/0
Mucor	0/0	91/22	0/0	0/0	58/13	0/0	0/0	149/35	0/0	149/35
Oospora	21/0	43/0	0/0	11/0	37/0	0/0	32/0	80/0	0/0	112/0
Penicillium	1344/116	434/76	769/149	1035/95	318/49	518/101	2379/211	752/125	1287/250	4418/586
Stemphylium	177/9	0/0	0/0	112/8	0/0	0/0	289/17	0/0	0/0	289/17
Sterile hyphae	67/0	3/0	0/0	27/0	4/0	0/0	91/0	7/0	0/0	98/0
Unidentified	0/0	4/0	0/0	1/0	1/0	0/0	5/0	1/0	0/0	6/0
Totals	2276/171	693/135	1562/304	1698/135	510/89	1080/200	3974/306	1203/224	2642/504	7819/1034

*Colony count during summer given in upper part of rectangle, winter in lower part.

TABLE X. CLIMATIC CONDITIONS ON DATES OF EXPOSURES

Date	Mean Temperature	Wind, m.p.h.	Precipitation
July 20	64	2-5	none
27	76	15-20	none
Aug. 3	81	10-15	trace
10	79	8-10	none
17	80	8-12	none
24	80	6-8	trace
31	76	10-11	none
Sept. 7	77	6-9	none
14	72	6-14	none
21	73	30-35	none
28	58	8-12	none
Oct. 5	66	10-12	none
12	68	5-9	none
18	68	10-11	none
26	66	7-11	0.11
Jan. 4	32	20-25	trace
11	30	10-12	none
18	7	8-10	none

wise, there seemed to be no essential differences between the mold flora of the different locations during the summer and winter months. Again, as may be seen from Table VIII, there was little difference in the relative percentages of each mold on potato-glucose agar and Sabouraud's agar.

Table IX is a condensation of Tables I, II, V, and VI. From this table, it can be seen that: *Alternaria* was present in the outdoor air and in the dusts but not in the indoor air during both the summer and winter; *Mucor* was found exclusively in the indoor air in both surveys; *Oospora* was present in both the outdoor air and the indoor air but not in the dusts during the summer, and was not isolated at all during the winter; *Stemphylium* was found only in the outdoor air during both the summer and winter; *Aspergillus* and *Penicillium* were the most frequent and widely distributed genera in both the summer and winter surveys.

A record, Table X, was kept of the mean temperature, wind velocity and preciptation for each date of exposure. Other than the differences in results in the summer and winter surveys, already referred to, possibly due

to differences in temperature, there seemed to be no significant effects produced by changes in weather.

Newton et al, in their survey, found that *Alternaria* was more prevalent in outdoor air than in indoor air and more prevalent in indoor air than in

TABLE XI. MOLDS FOUND IN ONE RESIDENCE BUT NOT IN THE OTHER

	Southwest	Southeast
Indoor air	Aspergillus niger Penicillium frequentans —	— — Aspergillus versicolor
Dust	Alternaria geophilia* Penicillium frequentans Aspergillus spp. Alternaria spp.** —	— — — — Aspergillus versicolor

*Not found in the January survey.
**Found only in the January survey.

house dusts. This survey of Lexington only, indicates that *Alternaria* is present more often in dusts than in outdoor air and not at all in the indoor air. Newton et al also found *Hormodendrum* in large numbers in central and western Kentucky, while the present survey revealed none at all in Lexington.

These discrepancies may be explained by the fact that this survey was confined to one city while that of Newton et al covered a relatively large area in which Lexington was only one of many communities studied. Again, as is apparent from the present survey, there are distinct differences in the mold flora of various locations within Lexington, and it is possible that *Hormodendrum* and other types of molds would have been found if this survey had included the same exposure point as did that of Newton et al. Also, Newton et al made their surveys in January and in March, while the present surveys were made in the late summer, early autumn and January.

From the results obtained in this study, it would appear that potato-glucose agar would be more satisfactory than Sabouraud's agar for an accurate quantitative survey of an area. However, in order to determine the mere presence or absence of various mold species, it would make little difference which medium was employed.

Of interest is the observation that certain species of molds that were found in one residence were not found in the other. As shown in Table XI (compiled from tables I, II, V, and VI) *Aspergillus niger* and *Penicillium frequentans* were found in the indoor air in the southwest residence but not in the southeast, whereas *Aspergillus versicolor* was found in the indoor air in the southeast residence but not in the southwest. These differences in mold distributions were shown consistently on both media in both the summer and winter surveys. *Penicillium frequentans, Alternaria*

geophilia, Aspergillus spp., and *Alternaria* spp. were found in the dust in the southwest but not in the southeast residence whereas *Aspergillus versicolor* was found in the dust in the southeast but not in the southwest residence. *Penicillium frequentans* and *Aspergillus versicolor* were found on both media and in both summer and winter. These findings emphasize the importance of making mold determinations at the house and the immediate surroundings of patients suspected of being sensitive to molds.

It is to be recommended that, within an area to be studied, various locations be sampled in order to determine more accurately and completely the mold flora. Since there is also a difference in the content of outdoor and indoor air and dust, these sources should all be included in the survey.

Since the major types of molds isolated during the summer and winter were virtually the same, a qualitative study need not be extended unduly. However, if a quantitative one is made, it should be conducted over a period of at least one year in order to determine the seasonal variations in numbers of molds isolated.

SUMMARY

A study has been made of the distribution of molds in indoor air, outdoor air, and house dusts from several sites in Lexington, Kentucky, on a large number of samples, using both Sabouraud's agar and potato-glucose agar. The results of this study have revealed the following:

1. *Penicillium* and *Aspergillus* were the most frequently encountered mold genera in both summer and winter from all sources of sampling.

2. *Mucor* was found exclusively in the indoor air.

3. *Monilia* and *Stemphylium* were found exclusively in the outdoor air.

4. *Alternaria* was present only in the outdoor air and in the house dusts. It was more prevalent in the summer than in the winter.

5. *Oospora* was present only in the air, not in the dust.

6. The air counts were lower during the winter than during the summer, although the dust counts showed no change.

7. There was no significant effect of any climatic condition except possibly temperature on the numbers or types of mold in the air.

8. Potato-glucose agar appeared to be more satisfactory for a quantitative study than Sabouraud's agar, although Sabouraud's is satisfactory for qualitative work.

9. Mold surveys for any region should include the examination of outdoor air, indoor air, and dust from several sites in that region.

10. The finding of different species of molds in two residences points to the importance of making mold determinations at the home and the immediate surroundings of patients suspected of being sensitive to molds

(References on Page 228)

A STUDY OF THE ANTIGENICITY OF ATOPIC REAGIN

M. SCHERAGO and MARGO HASSON

Lexington, Kentucky

STUDIES on the antigenicity of antibodies have been made by a number of investigators. Claims of successful anti-antibody production have been made by Pfeiffer and Friedberger (1903) working with goat anticholera serum, Bordet (1904) working with rabbit anti-ox blood hemolysin, Yanagihashi (1928) working with rabbit amboceptor for sheep red cells, Keilhack (1935) working with rabbit precipitin, Barany (1935) working with horse and cow diphtheritic antiserum, and Foster, Scherago and Weaver (1940) working with rabbit *Salmonella pullorum* agglutinins. On the other hand the results obtained by Salfeld and Weichsel (1937) with diphtheria antitoxin, Humphries, Scherago and Weaver (1941) with syphilitic reagin, Treffers and Heidelberger (1941 a, b) with rabbit pneumococcus antiserum, and Kass, Scherago and Weaver (1942) with enzyme purified diphtheria antitoxin, cast some doubt on the antigenicity of antibodies.

Since no studies on the antigenicity of atopic reagin appear to have been made, it was thought worth while to make such a study.

EXPERIMENTAL

Experimental Approach.—Rabbits were injected with reagin containing sera from untreated hay fever patients that were known to be sensitive to short ragweed pollen. At the termination of the injections a portion of the antiserum obtained from each rabbit was absorbed with pooled normal human sera of blood groups A, O, and B, in order to remove any precipitins to normal human blood serum antigens. In addition, another portion of antiserum from each rabbit was absorbed with homologous reaginic serum to remove all the precipitins that had been produced.

To determine whether antibody to reagin had been produced, the portion of each rabbit antiserum that had been absorbed with normal human serum was mixed with varying dilutions of the homologous reaginic serum, and the mixtures were injected intradermally into normal* individuals. Twenty-four or forty-eight hours later, each skin site was tested with the homologous atopen to determine whether the rabbit antiserum had neutralized the reagin, as indicated by a negative skin reaction. In addition, the portion of each rabbit antiserum that had been absorbed with the homologous reaginic serum was injected into the same individuals, followed in twenty-four or forty-eight hours by the injection of atopen, to see if the reaginic serum had absorbed out any antibodies against reagin, as indicated by a

From the Department of Bacteriology, University of Kentucky.
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Dr. Scherago is an Associate Member of The American College of Allergists.

*Normal refers to persons who gave no history of allergy and who did not react to the atopen when it was injected into an unsensitized skin site.

negative skin reaction. Control injections were made with each reaginic serum, the absorbed rabbit sera, normal rabbit serum and the atopen.

Preparation of Materials.—

1. Reaginic sera. Reaginic sera from two untreated hay fever patients were employed in this investigation. One of the sera (X) was obtained from Dr. Kenneth P. Mathews of the University of Michigan, Ann Arbor, Michigan, the other (Y) from the Long Island College of Medicine, Brooklyn, New York. Serum X was from a twenty-two-year-old man who was sensitive to short ragweed; serum Y was from a twenty-four-year-old man who was also sensitive to short ragweed.

Approximately 50 ml. of serum had been collected aseptically from each of the patients, in sterile rubber stoppered bottles. Soon after each serum was received at the laboratory, it was sterilized by filtration through a sterile No. 02 Selas filter and dispensed into two sterile rubber stoppered vials which were placed in the refrigerator until further use. Immediately after filtration the filtrate was tested for sterility by streaking one drop of it on a blood agar slant and one on a nutrient agar slant. The tubes were incubated at 37° C. and observed for four days. No growth was produced by any of the filtrates.

2. Normal rabbit sera. The normal rabbit sera used in the investigation were obtained from animals that had not been previously used for experimental work. The serum from each rabbit was sterilized by filtration through a Swinny syringe type filter, tested for sterility as described for the preparation of the reaginic sera, placed in a sterile rubber stoppered vial, and stored in the refrigerator.

3. Normal human serum. Samples of normal human serum were obtained from nine persons, three each from blood groups A, B, and O, who gave no history of allergy. Twenty milliliter volumes of blood were obtained from one of the cubital veins and the sera were separated, using the same procedure as that used in separating the rabbit sera, pooled, and stored in a sterile rubber stoppered glass bottle in the refrigerator.

4. Allergenic extract. The short ragweed extract used in the investigation was obtained from Dr. Kenneth R. Andrews of Lexington, Kentucky. It was diluted with sterile physiological saline to yield a final dilution of 1:5000. This dilution was employed for all skin testing. The extract was stored in a sterile rubber stoppered vial in the refrigerator. Fresh dilutions were prepared as needed.

Human Subjects for Prausnitz-Küstner Tests.—Only persons who gave no history of allergy and who gave negative skin reactions to the test atopen were used for the Prausnitz-Küstner tests. Each reaginic serum was tested on two persons.

Detail of Experiments.—

1. Preliminary procedures. (a) Passive transfer tests for the presence of reagin in the patients' sera.

In order to determine whether the two samples of sera from the allergic patients selected for this investigation contained reagin each serum was tested by the Prausnitz-Küstner method on two normal recipients. Both sera gave positive Prausnitz-Küstner reactions.

Each reaginic serum was retested every three weeks during the course of the investigation in order to see whether the reagin was diminishing in strength. At no time during the course of the investigation was there any evidence of a reduction in the strength of the two sera.

(b) Production and titration of rabbit antisera.

The immunization procedure that was employed in the preparation of the antisera against the reaginic sera was a modification of the method used by Dean and Webb (1926). Each of two young male rabbits was given two injections a week for four weeks with the reaginic serum against which it was to be immunized. The first two injections were given intravenously, and the six subsequent ones intramuscularly.

On the tenth day after the last injection, trial bleedings were obtained from the rabbits and the precipitin titers of their sera to the reaginic sera were determined by the micro-precipitin method.

The titer of the antiserum against reaginic serum X was found to be 1:1,600 and of the antiserum against reaginic serum Y, 1-3,200. Because these antibody titers were considered to be inadequate, a second series of two intramuscular injections a week for three weeks was given each animal after the animals had been given a rest period of five weeks. An outline of the schedule of injections is given in Table I.

TABLE I. SCHEDULE OF INJECTIONS OF REAGINIC SERUM INTO RABBITS

Feb.	27	3 c.c.*
Mar.	2	3 c.c.*
	5	3 c.c.
	8	2 c.c.
	11	2 c.c.
	14	2 c.c.
	17	1 c.c.
	21	1 c.c.
	31	trial bleeding
April	26	2 c.c.
	29	2 c.c.
May	2	1 c.c.
	5	1 c.c.
	8	0.5 c.c.
	11	0.5 c.c.
	21	trial bleeding

*The first two injections were given intravenously; all the others were given intramuscularly.

Ten days after the last injection of the second series, a few milliliters of blood were drawn from the marginal ear veins of the surviving rabbits, and the precipitin titers of the sera were determined. This time the antiserum against reaginic serum X had a titer of 1:6,400, and the antiserum against reaginic serum Y had a titer of 1:12,800.

Although the precipitin titers were not as high as was desired the small amounts of the reaginic sera that were left had to be conserved for the rest of the experiment and could not, therefore, be spared for additional injections of the rabbits to increase the precipitin titers. The animals were, therefore, bled from the heart on the day of the trial bleeding. Approximately 70 ml. of blood were collected from each animal. The blood was allowed to stand at room temperature for one hour, after which it was rimmed with a glass rod and centrifuged at 1,200 r.p.m. for fifteen minutes. The serum was separated and placed in rubber-stoppered bottles and stored in the refrigerator.

(c) Absorption of the rabbit antisera.

Portions of the rabbit antisera were absorbed with normal human serum in order to remove antibodies to the proteins present in normal blood. For this purpose a mixture of normal sera from blood groups A, O, and B were used. For the absorptions, the procedure of Cumley and Irwin (1943) was followed.

Absorptions were also carried out on portions of the rabbit antisera with homologous reaginic serum. The purpose of these absorptions was to remove all the antibodies in the rabbit antisera, including the anti-reagin antibody if it was present. These absorptions were to serve as controls on the previous absorptions, since there was the possibility that anti-reagin antibody would be carried down with the normal serum antibodies (co-precipitated) in the absorption process. If the skin reactions with the rabbit antisera absorbed with normal human serum proved to be positive, the question would arise whether anti-reagin antibody had been present in the rabbit antisera. The removal of all the antibodies to the reaginic sera would help to clarify this point. If no antibody to reagin was induced, then the antisera absorbed with reaginic sera would contain free reagin and corroborate the results obtained with the antisera absorbed with normal human serum.

After each rabbit antiserum had been absorbed it was concentrated to its original volume by placing it in a sterile sausage casing, and evaporating it with the aid of an electric fan.

The concentrated antisera were sterilized by filtration through Selas 02 filters, dispensed in rubber stoppered bottles, and placed in the refrigerator until further use.

For the sake of convenience, the portions of the rabbit antisera that were absorbed with normal human serum were designated ARAN, followed by the letter of the reaginic serum with which the rabbits had been immunized, i.e., ARAN-X and ARAN-Y. Similarly, the portions of the rabbit antisera that were absorbed with their homologous reaginic sera were designated ARAH-X and ARAH-Y.

2. Prausnitz-Küstner tests to determine the presence of antibody to reagin in ARAN.

In order to determine whether the rabbit antisera, that had been ab-

sorbed with the pooled normal human sera, possessed anti-reagin that would neutralize reagin, four series of intradermal injections were made into normal recipients for each of the two samples of rabbit antisera. One hour before the initial injections were to be made, the materials for each of the four series of injections were prepared as follows:

Series A. Reaginic serum undiluted and diluted 1:5, 1:10, 1:20, and 1:80 with physiological saline.

Series B. Mixtures of equal volumes of ARAN and of homologous reaginic serum undiluted, and diluted 1:5, 1:10, 1:20, and 1:80, making the final dilutions of homologous reaginic serum 1:2, 1:10, 1:20, 1:40, and 1:160.

Series C. Mixtures of equal volumes of pooled normal rabbit serum and of reaginic serum undiluted, and diluted 1:5, 1:10, 1:20, and 1:80, making the final dilutions of reaginic serum the same as in Series B.

Series D. Two portions of 0.1 ml. each of previously prepared ARAH. The mixtures were shaken at various times during the hour to insure adequate distribution of the components in them. The normal rabbit serum used in this experiment was a pool of the sera from two animals.

The purpose of Series B was to determine whether the reagin had been neutralized by an anti-reagin antibody in ARAN. Into one control site (6) in this series ARAN diluted 1:2 with reaginic serum was used for the initial injection and physiological saline was substituted for the atopen in the second injection, to rule out any non-specific reactions. Into a second control site (7) in this series ARAN alone was used for the initial injection, to rule out any non-specific reaction between it and atopen.

Series A, C, and D were all control series. Series A was a quantitative Prausnitz-Küstner test and the reactions obtained in this series were to serve as a basis of comparison for those obtained in Series B. Into one control site (6) in Series A undiluted reaginic serum was used for the initial injection and physiological saline was substituted for the atopen, to rule out any non-specific reactions. Into a second control site (7) atopen alone was injected to make sure that the recipient was not skin sensitive to the atopen.

The purpose of Series C was to make sure that the normal rabbit serum itself did not neutralize the sensitizing ability of the reagin, at least not to the same extent as the anti-reaginic serum, so that any inhibition of the sensitizing ability of reagin in Series B could be unequivocally attributed to an antibody to reagin. Into one control site (6) in this series normal rabbit serum diluted 1:2 with reaginic serum was used in the initial injection and physiological saline was substituted for the atopen in the second injection, to rule out any non-specific reactions. Into another control site (7) normal rabbit serum alone was used for the initial injection to see if the rabbit serum itself would react with atopen.

The purpose of Series D was to make certain that the suspected antibody to reagin was not precipitated along with the normal human serum antibodies in the absorption procedure. If positive reactions were observed in

TABLE II. SAMPLE PROTOCOL OF THE FOUR SERIES OF INJECTIONS

Site No.	Initial Injections				Second Injection
	Series A	Series B	Series D	Series D	
	0.1 ml. reaginic serum	0.1 ml. of mixture of equal volumes of ARAN and reaginic serum diluted.	0.1 ml. of mixture of equal volumes of normal rabbit serum and reaginic serum diluted.	ml. of ARAH	ml. of atopen
1	undil.	undil.†	undil.†	—	0.02
2	1-5	1-5	1-5	—	0.02
3	1-10	1-10	1-10	—	0.02
4	1-20	1-20	1-20	—	0.02
5	1-80	1-80	1-80	0.1**	0.02
6*	undil.	undil.	undil.	0.1**	0.02***
7*	—	0.1 ml. ARAN alone	0.1 ml. normal rabbit serum	—	0.02

*Controls within the individual series.
**These injections were made at sites corresponding to sites 1 and 2 of the other three series, and are therefore designated as sites 1 and 2 in the text.
***0.02 ml. of physiological saline was substituted for the atopen.
†The final dilutions of reaginic serum were twice those listed.

both Series B and D comparable to Series A, it would be established that no antibody to reagin had been induced. On the other hand, if the reaction in Series B were positive while Series D was negative it would be an indication that co-precipitation had occurred in the preparation of ARAN. Into one site (2) of Series D ARAH was used in the initial injection and physiological saline was substituted for the atopen, to rule out any non-specific reactions.

The injections were made on the backs of the recipients to facilitate comparison of the reactions. The materials for the four series of injections were introduced into sites on the skin in four parallel vertical columns down the back and labelled with black ink. All tests were done in duplicate.

Immediately after the initial injections of the mixtures of reaginic serum and ARAN, and of reaginic serum and normal rabbit serum, and of ARAH, wheals and erythemas appeared at the sites of the injections in all the recipients. These reactions changed gradually, until purplish red areas of from 25 to 30 mm. in diameter remained after one hour. The color faded entirely in two recipients (E. E. and N. S.) within twenty-four hours, while in the other two recipients (C. C. and D. H.) the purplish red areas gradually shrank in size so that at forty-eight hours they were from 7 to 11 mm. in diameter. On the other hand, at the sites that were injected with reaginic serum alone there was only a slight reddening of the skin immediately after the injections, which disappeared within five to ten minutes.

Twenty-four hours after the initial injections the sites in recipients E. E. and N. S. that were to receive the atopen were injected with it, and forty-eight hours after the initial injections the corresponding sites in recipients C. C. and D. H. were injected with atopen. The atopen used had, on a previous occasion, elicited a Prausnitz-Küstner reaction in sites that had been sensitized with the reaginic sera employed in this experiment. Site

TABLE III. MEASUREMENTS OF THE CUTANEOUS REACTIONS OBTAINED

Injection series	Site No.	Tests with Serum X				Tests with Serum Y			
		Recipient C.C.		Recipient D.H.		Recipient E.E.		Recipient N.S.***	
		15 min.	30 min.	15 min.	30 min.	15 min.	30 min.	15 min.	30 min.
A	1	8x9	7x7	12x11	15x12	12x14	15x15	4x5	5x5
		24x38*	24x32	55x44**	50x38	35x38	20x17	7x7	5x5
	2	7x9	6x7	10x11	13x10	10x12	12x10	4x5	5x5
		22x24	22x26	50x75**	44x32	28x22	20x10	12x8	20x10
	3	5x10	7x8	7x7	8x11	5x8	5x5	5x6	5x4
		20x22	21x16	43x29	40x29	14x10	10x10	20x26	20x25
	4	4x8	5x6	6x7	8x7	6x9	5x7	6x5	6x5
		12x20	17x20	40x31	36x28	10x22	14x9	27x16	30x20
	5	5x6	5x7	5x7	8x6	3x6	5x5	2x4	neg.
		10x10	11x9	40x28	39x28	3x6	5x9	2x4	
	6	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	7	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
B	1	neg.	7x7	10x8	neg.	neg.	neg.	neg.	neg.
			20x16	45x35					
	2	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	3	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	4	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	5	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	6	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	7	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
C	1	6x8	7x8	7x6	10x10	6x6	5x6	5x3	5x4
		12x14	30x22	45x30	45x32	14x11	10x7	22x14	20x10
	2	6x6	8x7	5x4	neg.	neg.	neg.	6x7	neg.
		6x6	10x11	35x30				6x7	
	3	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	4	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	5	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	6	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
	7	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.
D	1	neg.	7x7	5x5	4x5	neg.	neg.	neg.	neg.
			15x15	30x20	30x24				
	2	neg.	neg.	neg.	neg.	neg.	neg.	neg.	neg.

*Wheal in mm x mm / erythema in mm x mm.
**The erythema of sites 1 and 2, Series A overlapped and were hard to measure.
***Site 1, 2 and 3 in Series A were difficult to locate for the second injection (atopen), since the recipient had washed off the ink label. Thus, some sites were probably missed when atopen was injected.

6 in each series received physiological saline as did one unsensitized site (site 7) in Series A. A sample protocol of the injections given each recipient is shown in Table II.

The reactions were observed fifteen and thirty minutes after the administration of the atopen (or saline). At each reading Kodachrome photographs were taken. The wheals and erythemas were measured and the two greatest diameters of each were recorded. The measurements are given in Table III. The skin reaction values were obtained by adding the four measurements. The results of the skin reactions are recorded in

TABLE IV. REACTION VALUES OF CUTANEOUS REACTIONS

Injection Series	Site No.	Values with Serum X in Recipient				Values with Serum Y in Recipient			
		C.C.		D.H.		E.E.		N.S.	
		15′	30′	15′	30′	15′	30′	15′	30′
A	1*	79	70	122	115	99	67	23	20
0.1 ml. reaginic serum.	2	62	61	146	99	72	52	29	40
	3	57	52	86	88	37	30	57	54
	4	44	48	84	79	47	35	54	61
	5	31	32	80	81	18	24	12	—
	6	—	—	—	—	—	—	—	—
	7	—	—	—	—	—	—	—	—
B	1	—	50	98	—	—	—	—	—
0.1 ml. of mixture of = vol. of ARAN** and reaginic serum.	2	—	—	—	—	—	—	—	—
	3	—	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—	—
	5	—	—	—	—	—	—	—	—
	6	—	—	—	—	—	—	—	—
	7	—	—	—	—	—	—	—	—
C	1	40	67	88	97	37	28	44	39
0.1 ml. of mixture of = vol. of normal rabbit serum and reaginic serum.	2	24	36	74	—	—	—	26	—
	3	—	—	—	—	—	—	—	—
	4	—	—	—	—	—	—	—	—
	5	—	—	—	—	—	—	—	—
	6	—	—	—	—	—	—	—	—
	7	—	—	—	—	—	—	—	—
D	1	—	44	60	63	—	—	—	—
0.1 ml. ARAH***	2	—	—	—	—	—	—	—	—

—no reaction.
*1 = undiluted, 2 = 1:5, 3 = 1:10, 4 = 1:20; 5 = 1:80, 6 = undiluted (controls — received saline instead of atopen), 7 = no reaginic serum.
**Rabbit antiserum absorbed with normal human serum.
***Rabbit antiserum absorbed with homologous reaginic serum.

Table IV and in Figures 1 and 2. Figure 1 is a photograph of the reactions on one of the two recipients (D. H.) used in the experiment with reaginic serum X taken fifteen minutes after the injection of the atopen. (This recipient proved to be dermographic, which accounts for the erythema at sites 3 to 7 in Series B and C and at site 2 in Series D.) Figure 2 is a similar photograph of one of the two recipients (E. E.) used in the experiment with reaginic serum Y. The photographs that were taken of the reactions in the second recipient used with serum X and in the one used with serum Y did not differ materially from those in Figures 1 and 2, respectively. The appearance of the reactions was practically the same after thirty minutes in each recipient. Shortly thereafter, the wheals and erythemas gradually disappeared.

As may be seen from Table III, all four recipients gave positive reactions to the first five injections in Series A. In general, the size of the skin reactions diminished as the dilutions of the reaginic serum increased.

In series B, all the sites were negative when they were tested with short ragweed extract, except site 1 which was positive in both recipients (C. C. and D. H.) that received the mixture containing reaginic serum X undiluted. However, in recipient C. C. the reaction did not appear until the thirty-minute observation and in recipient D. H. the reaction at the fifteen-minute observation was weaker than that at site 1 in Series A, fading out by the time the thirty-minute observation was made. A possible explanation for the discrepancy in the reactions in site 1 between the two pairs of

recipients may be that the antibody titer to reagin (as judged by the precipitin titer) was higher in the ARAN that was mixed with reaginic serum Y (12,800), than in the one that was mixed with reaginic serum X (6,400). Assuming that antibody to reagin was present in the ARAN it seems

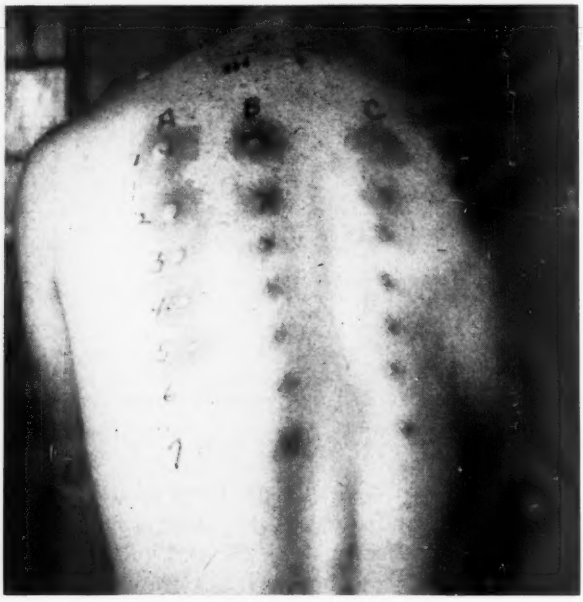

Fig. 1. Recipient D. H. injected with reaginic serum X taken fifteen minutes after the injection of short ragweed extract. For explanation of legends see Table III.

reasonable to expect that ARAN-Y would contain more anti-reagin antibody than ARAN-X, since the antiserum to reaginic serum Y had twice the precipitin titer of the antiserum to reaginic serum X. Therefore, ARAN-Y might be expected to neutralize more reagin than ARAN-X.

Contrary to expectations, the reactions in Series C did not parallel those in Series A. Positive reactions were observed only in site 1 of recipient E. E. and in sites 1 and 2 of the other three recipients. The sizes of these positive reactions were smaller, however, than those at corresponding sites in Series A, except for the reaction at site 1 in recipient N. S. Even in this recipient the reaction at site 2 (1:10) was smaller than the one at site 3 (1:10) in Series A. Apparently the normal rabbit serum had exercised an inhibitory effect on the Prausnit-Küstner reaction, especially where the higher dilutions of reaginic serum were used.

In Series D only sites 1 that had been injected with ARAH-Y were negative, while those that had been injected with ARAH-X were positive.

However, the reactions at sites 1 (Series D) that had been injected with ARAH-X were much smaller than those at the first four sites of Series A. In recipient C. C. the reaction was not observed until the thirty-minute reading. Furthermore, although the dilution of the reaginic serum in the

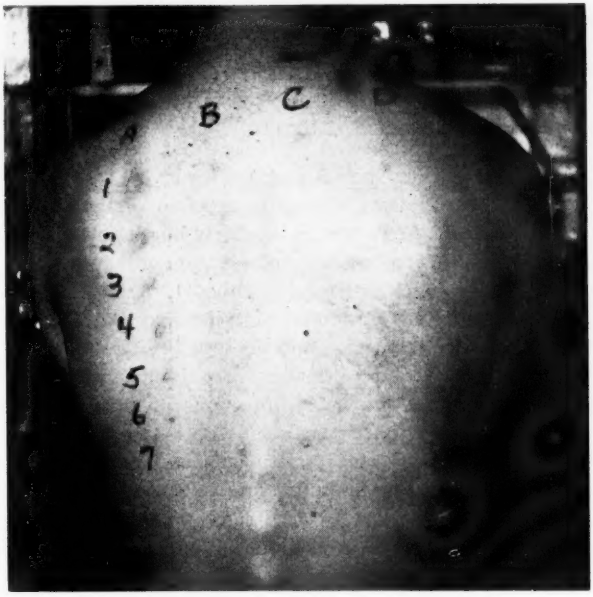

Fig. 2. Recipient E. E. injected with reaginic serum Y taken fifteen minutes after the injection of short ragweed extract. For explanation of legends see Table III.

ARAH-X was 1:2 it did not elicit as strong a skin reaction as the 1:20 dilution of reaginic serum in Series A.

DISCUSSION AND SUMMARY

Although the results of this experiment are not clear cut, they appear to indicate the possible production of reagin neutralizing antibody in the two rabbits that were injected with sera that had been shown to possess reagin. In both of the recipients (E. E. and N. S.) that were injected intradermally with the rabbit antiserum that had been absorbed with normal human serum and then mixed with reaginic serum Y, no skin reactions were elicited when the specific atopen was injected (Series B). Nor was there any reaction in these recipients at the sites (1 in Series D) that received a primary injection of the rabbit antiserum that had been absorbed with the homologous reaginic serum when the specific atopen was injected. The evidence for the production of anti-reagin antibody against serum Y would be quite convincing were it not for the negative skin reactions observed at

all the sites in Series C except the first in recipient E. E. and the first and second in recipient N. S. when the atopen was injected after the sites had received initial injections of normal rabbit serum mixed with reaginic serum. Nevertheless, positive reactions did not occur at those sites in this series that were given initial injections of the normal rabbit serum mixed with undiluted reaginic serum (sites 1) or (in one recipient) with reaginic serum that had been diluted 1:5 (site 2), and not at corresponding sites (Series B) that received initial injections of the anti-serum that had been absorbed with normal human serum and then mixed with reaginic serum.

In the case of the two recipients (C. C. and D. H.) that received initial injections of the rabbit antiserum that had been absorbed with normal human serum and then mixed with reaginic serum X the results are less convincing. In both recipients a positive reaction occurred at site 1 in Series B, in one case (C. C.) not until the thirty-minute observation and in the other (D. H.) at the fifteen-minute observation only to disappear at the thirty-minute observation. Furthermore, although the amount of reaginic serum (undiluted) that was introduced into sites 1 in Series B was greater than that (1-5) which was injected into the control sites (2, Series A) the reactions at the former sites were smaller. The results with reaginic serum X at the sites that received primary injections of the rabbit antiserum (against serum X) that had been absorbed with reaginic serum X (Series D) were also unconvincing. The reactions at these sites in both recipients were positive upon the injection of the specific atopen. However, the reactions at both sites (1, Series D) were much smaller than even those at the control sites that received the reaginic serum alone diluted 1:20 (sites 4, Series A.) As with reaginic serum Y, not all the reactions at the control sites (that received initial injections of normal rabbit serum mixed with reaginic serum X) were positive. Only the first two sites were positive.

The results of this investigation are far from conclusive, but they do point to the possible presence of reagin neutralizing antibody in the two rabbit antisera used in the experiment, especially in the one against reaginic serum Y.

We had hoped to be able to carry out the investigation with a larger number of reaginic sera. Unfortunately, it was very difficult to obtain the co-operation of allergists in sending us the large amounts (at least 50 ml. per patient) of reaginic serum which we needed from untreated allergic patients. It is hoped that this preliminary report will serve to bring us larger numbers of samples for further studies.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Kenneth P. Mathews of Ann Arbor, Michigan, and to Long Island College of Medicine, Brooklyn, New York, for the two reaginic sera, to Dr. Kenneth R. Andrews of Lexington, Kentucky, for the ragweed extract, and to Mr. George Scherr, of this department, for photographing the skin reactions.

(Continued on Page 291)

TREATMENT OF HAY FEVER WITH A COMBINATION OF A SYMPATHOMIMETIC AND AN ANTIHISTAMINIC DRUG

MARK H. MOTHERSILL, M.D., F.A.C.A.

Indianapolis, Indiana

EPHEDRINE is a sympathomimetic drug which was introduced about 1926 by Chen and Schmidt.[1] Until a few years ago ephedrine was probably more widely used for the symptomatic treatment of hay fever than any other compound. It was not perfect. Often it produced only partial relief, and efforts to increase the degree of relief by increasing the dose led to nervousness and wakefulness. The antihistaminic compounds which recently made their appearance were more effective in hay fever than ephedrine, and there was a tendency to replace ephedrine by antihistaminics in the symptomatic treatment of this disease. However, it seemed to us that instead of *substituting* antihistaminics for ephedrine it would be better to *combine* the two. The logic of such a combination is, first, that since both drugs are effective in hay fever, the combination might exert additive therapeutic action; and, second, that since antihistaminics as a rule produce sedation while ephedrine causes nervousness and wakefulness, these two side-effects might conceivably neutralize one another. There was also the possibility that the antihistaminics might potentiate the action of the sympathomimetic drugs.[6]

During the ragweed pollen season of 1948 we undertook a clinical comparison of twelve different preparations for the oral treatment of hay fever. Six of the twelve were antihistaminics, four were combinations of antihistaminics with sympathomimetics, one was a sympathomimetic alone, and one was a combination of an antihistaminic and a theophylline-containing compound. Approximately 100 patients who expected to have symptoms of ragweed pollinosis volunteered to take these drugs on successive days when they had symptoms and make reports on the relief and the side-effects. The work was done in the city of Indianapolis, which has higher ragweed pollen counts than most other cities in the country. This, we thought, might make the test more severe and the comparison more accurate.

The various drugs were prepared in white capsules so that their identity would not be known to the patients. They were numbered from 1 to 12 and were referred to throughout the season as "Drug No. 1," "Drug No. 2," et cetera. No one but the writer knew the identity of the preparations to which the various numbers referred. During the first week of August the patients were asked to come to the office and obtain their initial supply of drugs which consisted of eight envelopes numbered from 1 to 8. They also received instructions and a report blank. Each envelope contained what we thought would be an ample supply of capsules

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of that drug for one day's treatment. The patients were not to begin treatment until they developed symptoms of hay fever. Then they were to use capsules from Envelope No. 1 on the first day, from Envelope No. 2 on the second day, and so on. After having used each drug in the

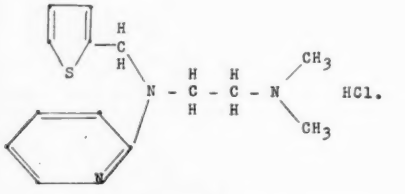

Fig. 1. Graphic formula of Histadyl.

series for one day, the patient was to start again with Drug No. 1 and go through the series a second time, omitting on this round any drugs that had proved unsatisfactory on the first. When the second round was finished, they began on the third round, provided they still had symptoms. On days when they had no symptoms they were to discontinue treatment. Incidentally, we observed that each patient seemed to have his or her own threshold pollen count above which symptoms developed. The threshold of one patient appeared to be a pollen count of less than ten. She began having symptoms during the first week of August and was still requiring treatment on September 30. Another patient had symptoms only for a week at the peak of the season.

At the end of each day's treatment the patients were to write on the report blank which we furnished them: (1) the date, (2) the number of the drug used that day, (3) the doses, (4) the degree of relief, and (5) the side effects. Once a week they were to present themselves at the hospital office with their written report of the previous week. At these visits questions were asked them in an effort to make interpretation of their report as accurate as possible, and they were then given another week's supply of drugs and another report blank.

When the season was completed, a large mass of data on twelve different preparations had been collected. Any effort to cover adequately the reports on the entire twelve would require a much longer paper than is here contemplated. Consequently, reports on only two of them, namely, Drug No. 3 and Drug No. 4, are being given. Drug No. 3 consisted of white capsules containing 25 mg. of Histadyl.* Drug No. 4 was also in white capsules of identical size and appearance and each capsule contained 25 mg. of Histadyl plus 8 mg. of Ephedrine Hydrochloride.

Histadyl is an antihistaminic drug which was investigated pharmacologically by Lee, Dinwiddie and Chen[6] and by Landau and associates.[4,5] Clinical studies were reported by Peirce,[7] Feinberg,[2] and Gay[3] and their

*Histadyl (Thenylpyramine, Lilly)

associates. Basically Histadyl is a dimethylethylene diamine to which are attached pyridyl and thenyl groups (Fig. 1). It is supplied as the hydrochloride of this base.

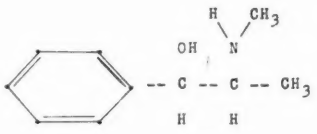

Fig. 2. Graphic formula of ephedrine.

DOSAGE

The dose was to be adjusted to the patient's requirements. The first dose of a drug which the patient had not taken previously was to be one capsule. If the relief obtained from this was insufficient and there were no side effects, the next dose was to be two capsules. If this gave incomplete relief and no side effects, the next dose could be three capsules, and so on. Later in the season when the patient took the same drug again he began the day with what had seemed to be the optimal dose previously. Toward the end of the season the dose was being adjusted more accurately and better results were being obtained. The doses varied from one to four capsules, the majority taking two capsules four to five times a day. In many instances the patient preferred to take two capsules with partial but satisfactory relief rather than to take three capsules and risk side effects. If side effects appeared without satisfactory relief, the patient was at liberty to discontinue further use of that number.

RESULTS

Originally 100 persons volunteered for treatment, but the number was reduced to sixty-seven for various reasons. Some of them were not sufficiently allergic to ragweed pollen to require treatment. In others the period of treatment was so brief that comparisons were impossible. Others found the task of following directions and making accurate reports too exacting.

In Table I it will be seen that the patients reported on a total of 145 treatment days with Histadyl and 147 treatment days with the combination of Histadyl and ephedrine. They were asked to report their results in five categories: (1) complete relief, (2) almost complete, (3) partial but satisfactory, (4) very little relief, and (5) no relief.

The sum of the first three categories, which would include all who obtained enough relief to call it satisfactory, was 87 per cent for Histadyl and 90 per cent for the combination. The incidence of complete and almost complete relief was 36 per cent for Histadyl and 48 per cent for the combination of Histadyl and ephedrine.

TABLE I. SUMMARY SHOWING DEGREE OF RELIEF IN THE TREATMENT OF RAGWEED POLLINOSIS

Degree of Relief	Histadyl		Histadyl, 25 mg., and Ephedrine Hydrochloride, 8 mg.	
	Number of Treatment Days	Per Cent of 145	Number of Treatment Days	Per Cent of 147
Complete	41	28%	63	43%
Almost complete	12	8%	8	4%
Fair to good	73	51%	61	41%
Very little	3	2%	3	2%
None	16	11%	12	8%
Total	145		147	
Relief ranging from fair to complete	126	87%	132	90%
Including almost complete and complete	53	36%	71	48%

SIDE EFFECTS

In the report blanks there was a column headed "Side effects." The patients were asked either to write "none" in this column or to describe the side effect, if any. The necessity of writing something in the column may have caused them to record a few discomforts which were trivial and a few that were coincidental. In Table II the side effects are listed in the language used by the patient in describing them. This table may aid in giving an insight into the nature and degree of the symptoms. Totals of thirty-four side effects for 145 treatment days with Histadyl and thirty-two side effects for 147 treatment days with the combination were reported. It will be seen that the percentage of patients having side effects with the combination was only slightly lower than with Histadyl alone. Qualitatively, however, the side effects were different.

In Table III the side effects are classified into six groups. The incidence of sedation was 15 per cent with Histadyl and 9 per cent for the combination. Nervousness, insomnia, and headache are grouped together because they are characteristic side effects of ephedrine. The incidence of these three was 2 per cent following Histadyl and 7 per cent following the combination.

DISCUSSION

This is a clinical rather than a pharmacological study. Pharmacologists have been of great value in advancing our knowledge of antihistaminic compounds, but any effort to predict from pharmacological figures which of two compounds will constitute the most satisfactory clinical treatment of hay fever is likely to be misleading. Men have many similarities to mice, but men are *not* mice. Hence the clinical test, particularly for a drug used as symptomatic treatment, is a more nearly final answer.

The incidence of sedation was reduced from 15 per cent to 9 per cent when the combination of Histadyl and ephedrine was used, but the incidence of nervousness, insomnia, and headache was increased from 2

TABLE II. SIDE EFFECTS IN THE LANGUAGE OF THE PATIENT

Symptoms	Number Reported with Histadyl	Number With Histadyl and Ephedrine
Slightly drowsy	3	3
Drowsy	16	9
Sleepy	3	0
Tired	0	1
Dopy	1	0
Slight headache	1	2
Headache	1	3
Slightly nervous	0	1
Nervous	1	1
"A little shaky"	0	1
Jittery	0	1
Could not sleep	0	1
Slight dizziness	0	2
Dizzy	3	1
Dryness of mouth	4	2
Nausea	0	1
Indigestion	0	1
Cramps?*	0	1
Diarrhea	1	0
Fever	0	1
TOTAL	34	32

*The patient herself inserted the question mark.

TABLE III. CLASSIFICATION OF THE REPORTS ON SIDE-EFFECTS

Type of Side Effect	Histadyl		Histadyl and Ephedrine	
	Number	Per Cent of 145	Number	Per Cent of 147
Sedation	23	15%	13	9%
Headache, nervousness, or insomnia	3	2%	10	7%
Dizziness	3	2%	3	2%
Dryness of mouth	4	3%	2	1%
Gastrointestinal symptoms	1	1—%	3	2%
Fever	0	0	1	1—%
Total	34	23%	32	21%

per cent to 7 per cent. A study of the patients' descriptions indicates that, as a rule, the side effects were not very severe.

Some individuals appear to be excessively responsive to stimulation by sympathomimetic drugs. As stated earlier, a total of twelve drugs were included in this study and five of them contained sympathomimetics. One of our patients picked out these five and suspected that each of them contained ephedrine because each one gave him a headache. The number of patients overresponsive to ephedrine was small, and these were better satisfied with Histadyl alone. The majority were better pleased with the combination.

SUMMARY

1. During the ragweed hay fever season of 1948 a group of sixty-seven patients reported on 145 treatment days with Histadyl and 147 treatment days with capsules containing 25 mg. of Histadyl and 8 mg. of Ephedrine Hydrochloride.

2. The two preparations were supplied in white capsules of identical appearance.

3. The incidence of satisfactory relief, ranging from fair to complete, was 87 per cent for Histadyl and 90 per cent for the combination.

4. The incidence of complete or almost complete relief was 33 per cent higher for the combination than for the antihistaminic alone.

5. The incidence of side effects classified as sedation was 15 per cent with Histadyl and 9 per cent with the combination.

6. The total incidence of nervousness, headache, and insomnia was 2 per cent during Histadyl therapy and 7 per cent when the combination was being given.

7. The majority of patients were better pleased with the combination.

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A WEEKLY MOLD SURVEY OF AIR AND DUST IN LEXINGTON, KENTUCKY

(Continued from Page 211)

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COMPARATIVE STUDIES OF CERTAIN ANTIHISTAMINE DRUGS

N. B. DREYER
Burlington, Vermont

IT is too commonly believed that histamine stimulates all smooth muscle. Experience shows that there are many exceptions to this generalization; for example, the elasmobranch intestine, mesentery, and uterus are completely unaffected by histamine. In contrast the teleost is very sensitive to histamine. In mammals there are wide variations in sensitivity. The white mouse and the rat are most refractory, whereas the guinea pig is most susceptible. Even within a mammalian species, the actions of histamine vary. These actions may be classified as motor, inhibitory, and secretory. In the human and the guinea pig, the uterus is stimulated to powerful contraction. The rat uterus, on the contrary, is relaxed by histamine. In mammals, with the exception of the guinea pig, the large intestine contracts more readily in response to histamine than the small intestine. Among the inhibitory effects are the arteriolar and capillary dilatation which cause the histamine wheal and flare in the skin and vasodepression. Its secretory effects are best illustrated by an increased gastric secretion. Following intra-arterial injection in carnivora, salivary secretion is stimulated.

The antihistamine drugs do not diminish or abolish with equal ease all of these various actions of histamine. They exert no influence on the gastric secretion by histamine, and while they do inhibit the histamine wheal and flare when applied locally, they do not do so completely when given orally. It is now generally agreed that these drugs compete with histamine at effector sites in accordance with the Langmuir adsorption isotherm.[5]

It should be emphasized that antihistamine drugs are different chemical substances which exhibit different pharmacological and clinical properties. To illustrate these differences, it may be noted that some of these drugs possess local anesthetic properties; they have atropine-like, antispasmodic, quinidine-like, Demerol-like, and musculotropic actions. And finally, some antihistamines sensitize to epinephrine while others desensitize.

The antihistamines have dual actions on some tissues as shown by their effects on striated muscle. In small concentrations, there is increased contraction due to indirect (nerve) stimulation. In high concentrations, indirect stimulation is suppressed, presumably because of block at the myoneural junction, but contraction is not inhibited upon direct stimulation of the muscle. Similarly, the antihistamines depress impulse transmission at autonomic ganglia. In the autonomic system, cholinergic responses are partially or completely depressed, depending upon the drug used, whereas adrenergic responses are usually undiminished and may even be potentiated with some drugs.

From the Department of Pharmacology, School of Medicine, University of Vermont.

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Other dual actions are observed with the antihistamines; for example, Neohetramine and Neo-Antergan in small doses depress intestinal motility, but in large doses they stimulate. Other drugs stimulate motility in small doses, but depress in large doses. Similarly, a dual effect on the blood pressure may be demonstrated with Trimeton and Neo-Antergan. Small

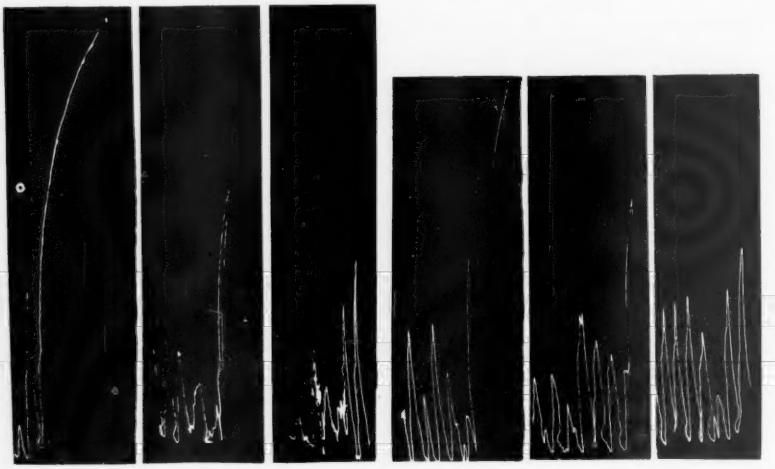


Fig. 1. Guinea pig uterus. Comparison of Anahist (A) and Inhiston (I) at concentrations of 1.8 and 3.6 mcgm. Histamine (H) at .2 mcgm. added to bath.

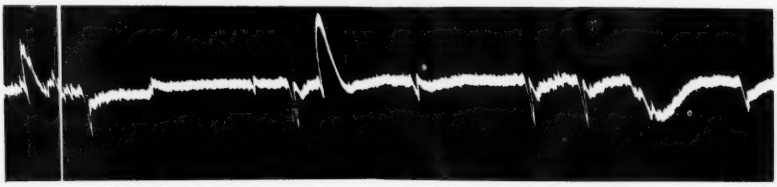
doses of these drugs cause a brief hypertension, but large doses cause vasodepression.

Recently, several antihistamine drugs were made available to the public without a prescription. Because of the limited pharmacological data reported, and since these drugs will now be used extensively in industrial medicine to reduce absenteeism due to the common cold, and since the drugs will be used by the public without medical supervision, it seemed desirable to compare some of the over-the-counter antihistamines.

Guinea Pig Ileum.—Tissues were suspended in a 30 c.c. bath of oxygenated Ringer-Locke solution at 37° C. Following the addition of histamine in amounts sufficient to evoke a sub-maximal response (0.5 to 4.0 micrograms per 30 c.c. bath fluid), the concentrations of Anahist and Inhiston required to counteract the histamine contraction were determined. The results with Anahist were the same as those previously reported.[4] Careful evaluation of Inhiston failed to reveal any difference in potency as compared with Anahist.

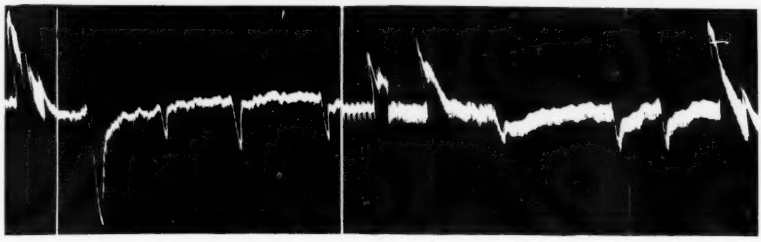
Guinea Pig Uterus.—Similarly studied on the isolated guinea pig uterus, both drugs again appeared to be equal in activity (Fig. 1).

Excised Tracheal Tissue.—Studied according to the method of Castillo and deBeer,[1] as described earlier,[4] both drugs at concentrations of .02 micrograms per c.c. of bath fluid produced a 26 to 27 per cent reduction of the histamine contraction. Here, again, no difference in activity was observed.



E H I I_2 H E I_3 H H I_4 H

Fig. 2. Dog—nembutal anesthesia, atropinized. Shows the potentiation of epinephrine (E), 2 ug. per kg. response following Inhiston (I) and the failure of Inhiston to abolish the hypotensive effects of .75 ug. per kg. of histamine (H). At I_4 9.5 mg. per kg. of Inhiston reduced but did not abolish the hypotensive effect of .75 ug. per kg. of histamine.



E H A_1 A_2 H E E I H H E

Fig. 3. Dog—nembutal anesthesia, atropinized. Shows the depression of the epinephrine (E) 2 ug. per kg. response following Anahist (A) and the increase in the epinephrine response following Inhiston (I) 5 mg. per kg. in spite of the presence of Anahist. Both Anahist and Inhiston diminished but did not abolish the hypotensive effect of .6 ug. per kg. of histamine (H).

Blood Pressure.—The potencies of both drugs in counteracting the effect of intravenous histamine were determined in atropinized dogs under sodium pentobarbital (30 mg. per kilo i.v.). At doses of 0.1 to 0.3 micrograms of histamine per kilo, both drugs appeared equally effective in abolishing the histamine vasodepression. At higher doses of histamine (0.5 to 1.0 mcg. per kilo, the vasodepression was never completely abolished by either drug (Figs. 2 and 3).

Capillary Permeability.—Recently, Lovejoy, Feinberg, and Canterbury[3] reported a capillary wheal-flare test. They believe that their test results parallel the clinical activity of antihistamine drugs. In view of their findings, the action of Anahist and Inhiston upon histamine-induced capillary permeability was studied intracutaneously in rabbits. Using the ex-

perimental design previously reported,[4] Anahist was found to be about twice as effective as the other drug.

Acute Toxicity.—Determined in the C. F. 1 strain of mice, the LD_{50} in mg. per kilo i.p. was found to be 96 for Inhiston (94-107 per cent limits of error), and 116 (93-108 per cent) for Anahist. In this test, the former appears to be significantly more toxic than Anahist.

Given the activity and the toxicity of a drug, one may compute a therapeutic index as the LD_{50} divided by the effective dose—50. It is evident from the foregoing data that Anahist would enjoy the better therapeutic index, since it is equal to or more active than Inhiston and less toxic. No attempt has been made to calculate therapeutic indices because they are not applicable to man and cannot be carried over to clinical practice. The recent advertising claims made on the basis of this time-honored laboratory statistic are misleading. Such use of the therapeutic index is to be regretted.

Blood Pressure Studies.—Anahist, in small or large doses, produces a hypotension of short duration. Inhiston, in small doses (up to 1 mg. per kilo), produces a slight hypertension without any increase in pulse rate in the atropinized or unatropinized animal. At the usual rates of injection, larger doses of this drug (2.5 to 5 mg. per kilo) cause a more prolonged fall in blood pressure than that produced by comparable doses of Anahist. This prolonged vasodepression may be due to an Inhiston depression of the myocardium.

It has been reported that Pyribenzamine and other antihistaminics enhance epinephrine responses[2] while Anahist does not.[4] In the present study, it was found that Inhiston in concentration of 0.5 to 2.5 mg. per kilo potentiates epinephrine (Fig 2). In contrast, epinephrine responses following Anahist were always diminished (Fig. 3). These results suggest that Anahist may more safely be used in hypertensive states.

Isolated Frog Heart.—In small concentration (1 microgram per c.c.), neither drug affected the Straub frog heart preparation. Larger concentrations (5 to 10 micrograms per c.c.), of both drugs caused an equal and well-marked diminution in systolic contraction. This action disappeared following changes of Ringer solution.

Isolated Guinea Pig Heart—Langendorf perfusion of 50 micrograms of Anahist caused myocardial depression with recovery. There was no change in coronary flow or heart rate. In the same preparation, 50 micrograms of Inhiston produced a more pronounced depression with a much slower recovery in amplitude (Fig. 4).

Cat Intestine In Situ.—Intravenous injections ot the drugs (0.1-0.5 mg. per kilo), in anesthetized cats (Chloralose 100 mgs. per kilo) produced

contrasting responses. As found earlier,[4] Anahist in small doses produced a depression of intestinal motility with recovery. Higher doses produced stimulation. Inhiston had a slight stimulant effect in small doses, while larger doses produced a prolonged depression. This depression of the gut can be counteracted by larger amounts of Anahist.

Fig. 4. Perfused guinea pig heart—Langendorf preparation. Depression of heart contractions with equal amounts of Inhiston above and Anahist below (50 mcgm. added to perfusion fluid).

Persistence.—Male guinea pigs (300 to 400 gm.) were given 50 mg./kg. of Anahist, Inhiston, and Chlor-Trimeton orally. The Chlor compound was included because of structural similarity and because it has recently been presented to the medical profession. At varying time intervals after administration of the drugs, a lethal dose of histamine (0.5 mg./kg. as base) was injected intravenously, and survival was taken to indicate the persistence of the drug in the animal. Judged in this way, Anahist remained in the animal for less than eight hours. This persistence is in keeping with clinically-accepted dosing schedules. Inhiston persisted in the animal for more than twenty-four hours, indicating that this drug will accumulate following repeated doses. The Chlor compound persisted for more than forty hours, indicating cumulation and the risk of possible organ pathology.

Repeating the experiment with a smaller dose (5 mg./kg.), animals were protected for shorter periods of time, but the same over-all picture obtained. The Chlor compound was the most persistent, Inhiston less persistent, and Anahist was the least persistent.

The persistence of these drugs was also determined in nephrectomized dogs under sodium pentobarbital (30 mg./kg.) by the ability of these drugs to counteract the vasodepression of intravenous histamine. Judged in this way, the persistence of the three drugs was essentially the same as described in the preceding experiments.

SUMMARY

It seems clear from the foregoing experiments and from the bulk of published evidence that the various antihistamine compounds are different

(Continued on Page 286)

WHAT IS TO BE OUR BASIC PROFESSIONAL RELATIONSHIP?

CARL R. ROGERS, Ph.D.

Chicago, Illinois

IT IS a very unusual experience for me to be invited to speak to a conference of allergists. I have no special knowledge of allergic conditions and no close knowledge of the problems the physician faces in dealing with these problems. In fact, insofar as the field of allergy treatment is concerned, I would like to make it clear at the outset that I have no experience in that realm, and nothing to offer to this group except that which arises out of the experience that I and my colleagues have had in attempting to deal with psychological problems. Since you, too, are dealing with syndromes which often have a large psychological component, it may be that we can find here an area upon which we can fruitfully think together. The phase of that area which I have chosen to discuss is the basic question as to what constitutes the most effective relationship with our patients or clients—the relationship from which they can obtain maximal help.

I should like first to say a few words about the relationship of the physician and patient in those situations which are clearly and almost solely organic. I realize that when an outsider tries to describe a profession he is apt to misrepresent it, and if I misrepresent this relationship I trust it will be brought out in the discussion. It seems to me that the element of primary importance in the physician-patient relationship in those situations where the problem is organic is the element of accurate evaluation of the patient by the physician. The physician, the expert, must adequately gather the data through history-taking, through physical examination, through laboratory tests. He makes his tentative interpretations and evaluations, checking these evaluations against further tests. The primary responsibility for the processes of diagnosis and treatment lies in the hands of the physician. The locus of evaluation resides primarily in him. He is continually asking himself such questions as: What does this sign mean? How shall I evaluate this symptom? What is my judgment of all the interrelated observations? In all of this process it is secondary or even immaterial whether the patient has any basic understanding of the illness or of the process of cure. The effectiveness of the relationship rests basically upon what goes on in the mind of the physician.

In dealing with organic disease and dysfunction this mode of approach has been so successful that one might say that the progress of medicine has been measured by the development of new evaluation procedures. The physician, with the aid of an increasing array of technicians, has learned how to make more accurate, more discriminating, and more complex evalu-

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ations. The more expert he has become in these judgments, the more he has been able to cope with the organic problems which his patients present.

With this impressive record of success, it has quite naturally been assumed that progress in dealing with psychological problems would follow the same pathway. Clinical psychologists and psychiatrists alike have tended to assume that if they could understand, diagnose and evaluate psychological conflicts and deviations with an accuracy equal to the physician's evaluations of organic conditions, then treatment of these psychic difficulties would be equally effective. Hence the enormous development, in both the psychological and psychiatric fields, of systems of classification of mental disorders, of complex methods of psychological measurement and diagnosis, and a great concern with the discovery of basic causes of conflict. I will not bore you with a detailed description of these developments.

On the whole this type of development has been disappointing, at least insofar as therapy is concerned. Many facets of human nature have been discovered, measured and classified, but effective help to the person has not necessarily resulted. The difficulties which have arisen seem to me to point up the difference between dealing with organic and psychological problems. I would describe the difficulties in these terms:

1. It has gradually come to be recognized that in psychological conflicts, improvement or cure can only come about through the individual learning for himself the causes of his behavior and learning for himself new ways of perceiving and reacting to these causes. If, in a particular neurosis, I know very accurately that the client's irrational reactions are due to a very strict early environment, and the introjection of perfectionist standards, with a consequent development of feelings of unworthiness and a repression of most of her spontaneous emotional reactions, all this knowledge on my part is of no help to my client. And if I should attempt to teach her this diagnosis, every therapist knows that an increased defensiveness would be the most likely result. As professional workers we have painfully realized that accurate evaluation in the mind of the expert is of practically no help to the client, in situations of psychological conflict and difficulty.

2. A second difficulty which has less frequently been commented upon is that there is some evidence that in situations of psychological difficulty, the very process of being evaluated by the expert is in itself detrimental rather than therapeutic. The person who has been informed, accurately enough, that he is a compulsive, or a rejecting parent, or that he has average intelligence, tends to lose, to a certain degree, his basic confidence in himself. Essentially he comes to feel that he cannot know himself, that only the expert can adequately evaluate him. Yet to damage his confidence in his ability to evaluate himself and his experience is to damage the very foundation upon which therapy must rest.

3. Still another difficulty lies in the fact that as psychotherapy spreads to an increasing number of people, certain philosophical questions come to assume greater importance. If, as the expert, I evaluate the strengths and weaknesses of this man's job relationship, marital relationship, and personal behavior, understand the causes of his difficulties, and set goals for his therapy, then almost inevitably I find myself choosing his values, or influencing his own choice of values. Shall he adjust to the status quo of his work situation or try to change it? Will therapy consist of his working out a better relationship with his wife or divorcing her? Is his behavior healthy or should I aim to change it? As I see it, insofar as we set for ourselves any such goals in therapy we enter the realm of values, and to a certain extent set ourselves up as arbiters of what is right. In a recent article which shocked some of my professional colleagues, I tried to spell out the implication of this point of view as I see it: that if it is accepted as sound, its eventual working out in the social milieu involves a basic philosophy of the control of the many by the self-selected few. I will not, however, belabor that point here.

What I am trying to point out thus far could be summarized by saying that a physician-patient relationship in which the role of the expert is to make accurate evaluation has been highly effective in dealing with organic problems; that it has been entirely natural that professional workers have assumed that the same approach would be equally effective in dealing with psychological problems; that experience seems to be indicating that actually it falls short in effectiveness in dealing with psychological conflict, that it may even be detrimental to treatment of the individual, and that it raises certain disturbing philosophical questions which cannot be lightly disregarded.

But if this type of relationship does not seem to provide the best mode of dealing with psychogenic problems, what is the alternative? Here it seems to me that most effective psychotherapies have been moving toward a different sort of relationship with the client or patient, and that client-centered psychotherapy has perhaps stated this relationship in its most extreme form. Whether it is the correct description of the effective relationship, only time and further experience and research can tell.

The sharp difference between the client-centered orientation and the physician-patient relationship we have been describing lies in the locus of evaluation. Rather than regarding the therapist as the evaluator, it is the client who is given the opportunity to evaluate, at deeper and deeper levels, the meaning and the significance of his behavior and his feelings. The responsibility rests in the client's hands for choosing whether to explore certain feelings or to leave them untouched, whether to proceed at a rapid rate of explanation or a slow one; it is his responsibility to discover the hidden relationships in his experience which we call insight; it is his responsibility to determine the way he will behave in the light of his new understandings. The responsibility of the expert lies in the difficult

and complex and emotionally demanding task of creating a psychological atmosphere in which the client can undertake this exploration and re-evaluation of self. The role of the expert is to create a relationship of such acceptance, understanding, warmth and respect that the individual feels safe from threat, and is freed to explore and understand those elements of his behavior and of himself which he has not understood.

As our practice of such a point of view has extended, as we have utilized it in dealing with a wider range of problems, the basic hypothesis upon which it rests has become evident with increasing clarity. This hypothesis is that the individual has within himself the capacity, latent if not evident, to understand those aspects of his life and of himself which are causing him unhappiness or stress or pain, and the capacity and the tendency to reorganize himself and his relationship to life in the direction of a socialized maturity, in such a way as to bring a greater degree of internal comfort. It is an hypothesis that the individual has a sufficient capacity to cope with life if a psychological atmosphere suitable for personal growth can be provided.

How does this sort of hypothesis work out in practice? In what way does the therapist create the atmosphere of which we have spoken? In what way does the client react? What is the process by which help is achieved? Much has been said and written about this, and a very brief description is likely to be misleading. Yet I shall try to put in a few words an account of the conditions which the therapist endeavors to create, and the process which is facilitated in the client.

1. Therapy seems most likely to occur when the therapist feels, very genuinely and deeply, a warm attitude of acceptance of and respect for the client *as he is,* with the potentialities inherent in his present state. This means a respect for the attitudes which the client now has, and a continuing acceptance of the attitudes of the moment, whether they veer in the direction of despair, or toward constructive courage, or toward a confused ambivalence. This acceptance is probably possible only for the therapist who has integrated into his own philosophy a deep conviction as to the right of the individual to self-direction and self-determination.

2. A second and corollary condition making for therapy is the complete willingness of the therapist for the center or locus of evaluation and responsibility to remain with the client. All judgments, all evaluations, all changes in evaluations, are left to the client. The counselor not only avoids voicing any evaluations of the client, or his behavior, or the meaning of his behavior, or the behavior of others—but by his immersion in the empathic process, tends to avoid *making* these judgments. Likewise responsibility is left with the client—whether it be responsibility for choosing the next topic of his conversation, or responsibility for some grave choice. This whole attitude on the part of the therapist is, if it is to be

effective, real and not forced. It is a basic willingness to help the client realize his own life in his own terms, and an unwillingness to attempt to take over the responsibility for his life or any part of it.

3. A third condition for therapy is the therapist's willingness and sensitive ability to understand the client's thoughts, feelings, and struggles, from the client's point of view. This ability to see completely through the client's eyes—to adopt his frame of reference—has seemed to be an important way of implementing the fundamental hypothesis, and is the basis for the use of the term "client-centered."

4. A fourth condition of therapy is that the counselor use only those techniques which implement these basic attitudes. Techniques are definitely secondary to attitudes, and seemingly poor technique may succeed if attitudes are sound, while we have not found the reverse to hold true. The most helpful techniques have seemed to be those which communicate something of the attitudes which the therapist deeply holds—his acceptance of the person as he is at this moment, and his empathic understanding of the client's attitudes as seen from the client's point of view.

These would seem to us to be the ways in which the therapist carries out his basic hypothesis. In one sense all of these conditions are wrongly described, since it is the experiencing of these by the client which is significant for therapy. It could be more truly stated that the conditions of therapy are met when the client experiences the respect and acceptance the therapist has for him, experiences an empathic understanding, experiences the locus of evaluation as residing within himself, experiences no sgnificant limitation on the expression of his attitudes. I have chosen however to describe the situation as the counselor perceives it.

When the therapist is successful in establishing these conditions, what is the process which is experienced by the client? I can only touch very briefly upon the most common characteristics of a rich and complex process.

In the first place the client rather quickly comes to experience this process as centered in him. He recognizes, in a way which comes to have more and more meaning, that he is working on himself. As one client puts it, "In counseling we were mostly *me* working on my situation as I found it. . . . I was the one that mattered, my thinking was the thing that was important, and my counselor was almost a part of me working on my problem as I wanted to work on it."

Another aspect of this process of therapy is the client's experience of exploration of attitudes, feelings, and perceptions. He tends first to talk about his symptoms, or about others, or about his environment. But as he feels the safety of the relationship, and recognizes that all his attitudes are accepted and understood, without evaluation of any kind, he finds himself talking more and more about himself. He also tends in the direc-

tion of discussing those experiences which do not seem to be a part of himself—experiences which he has not "owned" or which he has denied to awareness. Thus, in general, there is evidence that this exploration tends to go from symptoms to self, from others to self, from surface concerns to deeper concerns, from conscious feelings regarding self to feelings and experiences which have been denied to awareness because they are inconsistent with the self as it is organized.

As this exploration of self continues, he can, in the safety of the relationship, bring up and look at and perceive clearly, some of the feelings he has denied. This is a fearful and frightening part of the process, the degree of fear depending upon the degree of discrepancy between the attitudes he has consciously held and the feelings he has been denying. Seeing the relationship between these denied attitudes and his behavior is what may be thought of as insight.

As he recognizes more freely all the attitudes and experiences he has had, he finds himself reorganizing himself on the basis of these new perceptions. He can be himself more fully, in terms of these newly accepted perceptions. He finds his behavior moving in new directions which are consistent with this new idea of himself. He finds that he now has sufficient understanding and control of himself to free himself from the therapist and to move out on his own.

This is a bare outline of the process as we have seen it many times. Perhaps a very brief example may bring the outline to life. The wife of a lawyer came to the Counseling Center for help with an embarrassing physical symptom which seemed to crop up most frequently in situations where it would cause her and her husband the greatest degree of humiliation. Physicians could find no organic cause. At first she talked only of the symptom and its occurrences. She was very inhibited, stating that she wasn't sure she even had any feelings. She stressed that the symptom could have no relationship to her husband or the fact that she did not feel much liking for her oldest child. Little by painful little, she tentatively explored her desire to get her own way, her need to oppose her husband at times and her fear of doing so openly. She finally formulated for herself—first tentatively and then with assurance—the fact that the symptom was a way of attacking and humiliating her husband, and at the same time punishing herself for wanting to attack him. She could accept herself as a "stubborn wench" who held these attitudes. She recognized that she could not hold in her occasional antagonisms to her husband, but must find new channels for their expression. "After all, a temper tantrum would be better than this symptom" was her way of putting it. The symptom lost its uncontrollable force, and she was able to give up therapy, having made much improvement. Here we can see, in brief, the different elements of the process as I have described it: the recognition that this is a place where she can work on herself, the process of exploration which

(Continued on Page 286)

BLOOD LEVELS INDUCED BY PENICILLIN-ANTIHISTAMINE PREPARATIONS

F. J. MURRAY, BARBARA TAYLOR and MILTON J. FOTER
Cincinnati, Ohio

A VAST literature has accumulated on the subject of penicillin sensitivity and an excellent review of papers published up to October, 1948, is available.[2] This review deals with toxicity as well as sensitivity reactions.

From the evidence cited in the literature it is obvious that penicillin reactions occur most frequently in individuals who have had several courses of the antibiotic. Skin tests have been found unreliable in predicting the occurrence of reactions. The incidence and severity of such reactions has not been greater in allergic individuals than in non-allergic individuals.[1]

Twelve types of reaction have been reported following administration of penicillin and the over-all incidence of reactions has been reported at 2 to 5 per cent.[1]

With the variety of penicillin forms available and with the variations from lot to lot or from manufacturer to manufacturer, it has been stated that no clear-cut method of treatment is applicable to all patients.[2]

Brown[2] has concluded that the results of antihistaminic therapy are variable; others have indicated favorable results.[4,5,7] On the basis of the favorable reports Simon has reasoned that an antihistaminic should be of much greater value in preventing penicillin reactions.[8]

Using the antihistaminic Decapryn* (doxylamine) Succinate (dimethylaminoethoxy-methylbenzylpyridine), since he had found it to be the drug of choice in treatment of reactions, Simon concluded from his studies that the antihistaminic in combination with penicillin resulted in much fewer reactions, was practically painless on injection, and evoked blood levels comparable to those produced by penicillin alone.

Since Simon's work was carried out with crystalline potassium penicillin G aqueous with a Decapryn Succinate solution, it was thought desirable to study rabbit blood levels with other forms of penicillin preparations. The local anesthetic action of Decapryn was an apparent advantage in that it lessened pain of injection, but it was necessary to demonstrate that the advantage was not offset by reduced blood levels. The purpose of this paper is to show the effect, or lack of effect, of Decapryn on blood levels induced by various pharmaceutical forms of penicillin.

METHOD AND RESULTS

The dosage of penicillin administered to rabbits in these studies has been either 30,000 or 40,000 units per kilogram of body weight, the larger dose

From the Department of Bacteriology, Research Laboratories, The Wm. S. Merrell Company, Cincinnati, Ohio.
*Reg. Trade Mark of The Wm. S. Merrell Company.
Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

TABLE I. COMPARATIVE PENICILLIN SERUM LEVELS

Decapryn-Potassium Penicillin G in Oil—2% AL. Monostearate and Potassium Penicillin G in Oil and Beeswax (Romansky)

Sample	Rabbit	Hours—Units per cc.				
		½	1	3	6	24
Penicillin in Oil with 10 mg. Decapryn Base, per cc.	1	4.7	4.2	2.4	0.50	0
	3	9.0	6.4	2.6	0.19	0
	5	10.0	7.8	0.74	0.10	0
	7	6.7	5.6	2.6	1.50	0
	9	11.0	6.8	2.7	0.19	0
	11	2.0	7.0	2.8	0.92	0
	13	4.5	5.6	1.4	0.10	0
	15	6.5	10.0	1.4	0.35	0
	Median	6.6	6.6	2.5	0.27	0
Penicillin Control (Romansky Formula)	2	5.5	9.5	1.8	0.70	0.04
	4	7.2	8.0	1.3	0.35	0
	6	10.5	7.4	1.6	0.26	0
	8	5.0	5.9	0.59	0.15	0
	10	6.5	7.4	0.70	0.10	0
	12	7.5	7.6	1.0	0.34	0
	14	8.0	7.4	2.4	0.42	0
	16	11.5	3.2	0.82	0.23	0
	Median	7.4	7.4	1.2	0.30	0

TABLE II. COMPARATIVE PENICILLIN SERUM LEVELS

Potassium Penicillin G with and without Saline Decapryn Diluent

Sample	Rabbit	Hours—Units per cc.			
		½	3	6	24
Penicillin* with 5 mg. Decapryn Succinate per cc.	2	19.5	0.4	0	0
	4	27.7	2.2	—	0
	6	22.5	0.9	Dead	—
	8	20.5	1.6	0.07	0
	10	27.7	3.4	0.25	0
	12	21.0	1.0	0.06	0
	14	27.7	3.3	0.42	0
	16	27.7	1.6	0.18	0
	Median	25.1	1.6	0.12	0
Penicillin* Control	1	19.5	0.38	0	0
	3	27.0	10.50	0	0
	5	26.2	1.20	0	0
	7	27.7	0.42	0.19	0
	9	25.5	2.00	0.05	0
	11	30.0	0.50	0.04	0
	13	28.5	1.20	0	0
	15	27.7	1.30	0	0
	Median	27.3	1.20	0	0

*Peni-Crystin Trademark of The Wm. S. Merrell Co.

being employed for the fortified preparations. This dosage is based on a report that the percentage of animals showing concentrations of penicillin in the serum in excess of 0.05 units per c.c. following such dosage will equal the per cent of patients showing concentrations of penicillin equal to, or greater than, 0.03 units per c.c. following the injection of 1 c.c. (300,000, or 400,000 units) of the same preparation.[6]

All rabbit injections were made in the posterior left thigh muscle and all bleedings were by intracardial puncture. The assay method employed was the *Sarcine lutea* blood penicillin assay.[3] The average weight of the rabbits used was approximately 2.6 kilograms.

TABLE III. COMPARATIVE PENICILLIN SERUM LEVELS
Decapryn-Procaine Penicillin G and
Procaine Penicillin G for Aqueous Injection

Sample	Rabbit	Hours—Units per cc.		
		½	6	24
Procaine Penicillin* with Decapryn Succinate, 15 mg. per cc.	2	6.4	2.6	0
	4	5.4	1.9	0
	6	7.0	Dead	—
	8	4.4	3.2	0.13
	10	4.6	2.0	0
	12	3.8	1.8	0
	14	2.6	2.7	Dead
	16	6.2	2.4	0
	Median	5.0	2.4	0
Procaine Penicillin* Control	1	3.2	4.1	0.89
	3	6.0	5.2	0
	5	2.5	2.6	0
	7	4.2	4.0	0
	9	1.6	1.1	0.28
	11	3.6	2.0	0.28
	13	1.6	1.5	0.25
	15	1.4	1.6	0
	Median	2.8	2.3	0.12

*Parencillin—Trademark of The Wm. S. Merrell Co.

The Decapryn concentration in the various preparations has been set, in general, with regard to the difference in frequency of administration of the various penicillin preparations in humans.

The first comparison made in these studies was between the Romansky formula and crystalline penicillin G in oil with 2 per cent aluminum monostearate plus 10 mg. Decapryn Base† per c.c. As seen in Table I, there is little difference between levels or therapeutic duration induced by the two preparations.

Table II contains results of a comparison between crystalline penicillin G aqueous with and without a Decapryn Succinate diluent (5 mg. per c.c.). It can readily be seen that results with Decapryn were as good, or better than those obtained with control.

In the comparison between crystalline procaine penicillin with and without Decapryn Succinate (15 mg. per c.c.) the results in Table III indicate a higher peak for the Decapryn preparation. However, the difference in peaks is not likely to be of therapeutic significance and the number of control animals showing levels at twenty-four hours (four of eight) is not significantly different from the results with Decapryn (one of six). Applying the chi square test we find that such a difference could be due to chance at least once in five cases.

Table IV shows practically no difference between levels obtained with an aqueous fortified procaine penicillin with and without Decapryn Succinate (20 mg. per c.c.).

Procaine penicillin in oil has been evaluated with four levels of Decapryn Base added, 5, 10, 15 and 20 mg. per c.c. The comparison of control and

†Ratio of Decapryn Base to Succinate is 3:4.2.

TABLE IV. COMPARATIVE PENICILLIN SERUM LEVELS

Decapryn-Procaine Penicillin G Fortified with Potassium Penicillin G and Procaine Penicillin G Fortified for Aqueous Injection

Sample	Rabbit	Hours—Units per cc.		
		½	6	24
Procaine Penicillin Fortified* with 20 mg. Decapryn Succinate per c.c.	1	13.0	2.9	0.32
	3	8.2	3.6	Dead
	5	12.0	4.5	0
	7	13.0	3.5	0
	9	11.0	4.0	Dead
	11	12.0	2.7	0.17
	13	12.5	4.2	0
	15	8.8	4.1	0
	Median	12.0	3.8	0
Procaine Penicillin Fortified* Control	2	7.4	2.0	0.41
	4	13.0	2.9	0
	6	12.0	3.8	0
	8	6.3	2.4	0.09
	10	13.0	5.2	0.05
	12	13.0	3.8	0.11
	14	12.0	3.8	0
	16	13.0	4.2	0
	Median	12.5	3.8	0

*Parencillin (Fortified)—Trademark of The Wm. S. Merrell Company.

TABLE V. COMPARATIVE PENICILLIN SERUM LEVELS

Procaine Penicillin G in Oil—2% AL. Monostearate with and without Decapryn

Sample	Rabbit	Hours—Units per cc.		
		24	48	72
Procaine Penicillin* in Oil with 15 Mg. Decapryn Base per cc.	9	1.10	0.14	0.03
	10	0.55	0	0
	11	0.66	0.26	0.17
	12	0.70	0.14	0
	13	0.73	0.19	0.10
	14	0.89	0.30	0.14
	15	0.95	Dead	—
	16	0.90	0.17	0.03
	Median	0.81	0.17	0.03
Procaine Penicillin* in Oil Control	1	0.46	0.12	0.05
	2	0.46	Dead	—
	3	0.87	0.22	0
	4	0.80	0.16	0.04
	5	1.10	0.26	0.08
	6	0.96	0.13	0
	7	0.14	0.02	0
	8	0.56	0.09	0.03
	Median	0.68	0.13	0.03

*Parencillin (in oil)—Trademark of The William S. Merrell Company.

one Decapryn preparation (15 mg. per c.c.) is presented in Table V. Similar levels were stimulated by the two preparations and the same results were obtained with the other levels of Decapryn except that 20 mg. per c.c. seemed to prolong the therapeutic level, seven of seven animals having therapeutic levels at seventy-two hours.

In checking blood levels of ten patients switched from regular penicillin to Decapryn-Penicillin, Simon[8] reports four lower, two higher, and four about the same. Therapeutic results were similar for the two preparations.

In five of our studies we found the Decapryn-Penicillin products to be about the same as the penicillin controls. In one study mentioned the level stimulated by the Decapryn preparation was of longer duration than that of the control.

It is evident from the over-all comparisons that Decapryn has little or no effect on the blood levels induced by the various pharmaceutical forms of penicillin.

SUMMARY

1. Penicillin blood level studies were conducted on sera of rabbits injected with various penicillin preparations with and without an antihistaminic (Decapryn).

2. The administration of Decapryn Succinate with various pharmaceutical forms of penicillin produced blood levels of the same order as those obtained when penicillin is given with the customary diluents.

3. Decapryn Succinate did not appear to interfere with absorption of the penicillin.

The authors wish to express their appreciation to Miss K. Ludwig, Mrs. J. Scrugham and Mr. H. Ritter for assistance in the animal studies and to Miss M. Brosch for assistance with the assays.

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FILM AVAILABLE

Twenty additional prints are now available of the film "Allergy: Immunology and Treatment," prepared by the Medical Film Guild, New York, under the supervision of Leo H. Criep, M.D., Department of Immunology and Medicine, University of Pittsburgh. The film, in preparation for eighteen months, is a postgraduate course in allergy, made possible by a grant from Wyeth, Inc., Philadelphia, and Nepera Chemical Co., Yonkers, N. Y. It is available without charge to the profession through the firm of Wyeth, Inc.

Convention Echoes

PREPARATION OF PROGRAM PAPERS AND EXHIBITS

Excerpts from the Presidential Address
by

JONATHAN FORMAN, M.D.

EDITOR'S NOTE: President Forman's Presidential Address, unfortunately, was presented to the Board of Regents only, since time demanded that the length of the business meeting be curtailed, and President Forman obliged by giving up the time for his address. Included in the Presidential Address were such valuable suggestions concerning the submission of papers for future programs and the organization of scientific exhibits that the Board of Regents ruled that excerpts from the address be published in the ANNALS OF ALLERGY, and be sent out to all members when papers are solicited for the Seventh Annual Session to be held at the Edgewater Beach Hotel, Chicago, February 11-14, 1951. Let us read these suggestions over several times and show our loyalty to the College by personally endorsing and supporting these suggestions.

WHEN submitting the title of your paper to the program chairman for next year, and each of the following years, accompany it with a press release, some 250 words, of clear, concise, complete expositional writing containing all the facts that the public should know about the field in allergy of which you are writing, and then the logical arrangements of the particular contribution that you are making against this simple background of historical facts. This is imperative for the time element, if for no other reason. The period between the submission of your paper and its acceptance and the completion of the program is altogether too short for the Committee on Public Education to do a re-write job that is satisfactory, especially if they have to write and wire you three or four times because you have not made it clear in ordinary everyday language what your contribution is and how it is related to known facts. Nevertheless, we have no apologies for wide coverage of the recent College sessions in the metropolitan newspapers and the news magazines and weeklies throughout America. If we of the College, however, are to assume our just obligations to see that the people do get the facts about allergy, without distortion, and that they comprehend them, timing is important. You can help immensely if you will follow this suggestion of getting a press release to the Committee of Public Education as early as you possibly can.

And here are two suggestions about your paper that will add interest to our programs. First, *charts and slides that you use must illustrate,* for it is immoral to steal the time of so many people with slides which fail to illustrate because they are over-crowded. No matter how well they illustrate your paper, the rest of us will never know it unless we can read what you have placed upon these charts and slides from our place in the hall.

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

So for the sake of all concerned, please keep the wording *simple* and the type *large*. Slides should not take longer than one minute to read.

Now, about the paper itself. Our meetings will be made much more worthwhile in publication if we *shorten the papers and increase their number*. We must follow more and more the worthwhile scientific and learned Societies and train ourselves to give ten-minute papers. There is no point in clinical medicine and certainly no piece of research that cannot be presented within ten minutes if the essayist knows what he is talking about. In fact, eight minutes is adequate at the normal radio reading time of 140 words per minute, equaling approximately 1200 words. This does mean careful writing, meticulous editing and rewriting. It means writing one paper to read and another to publish. This last is very important. In setting up the program this year we ran into a very difficult misunderstanding because one of the discussants had only seen the paper that was to be read when he should have had full data. And so it is also the duty of the essayist to *furnish any formal discussant with a copy of the full paper.*

Incidentally, formal discussants are as a rule a great loss of time to the average person who is in attendance and, therefore, while we recognize the desirability of having as many discussants as possible appear on the program for the promotion of enthusiasm and esprit de corps, we should get more people on the program as essayists and not as discussants.

"We always," as Glenn Frank liked so well to warn us, "are inclined to *overestimate* the amount of information that our listeners have and to *underestimate* their intelligence." I urge, therefore, that you look into the results of the studies that are now going on in the subjects of readability and audience comprehension. Fleich's new book, "The Art of Plain Talk," or the work of Professor Edgar Dale at the Ohio State University will give you techniques for submitting your papers to test formulas which will identify at what level of education your paper is intelligible. The American farmer, for instance, in a recent survey was driven away from the United States Agricultural bulletins by the use of the word "relationships." But the word "relations" he knew and understood. Again in a recent survey made not too long after the death of Mr. Roosevelt, it was found that about 52 per cent of the people queried in a cross section of America had not heard about the United Nations. After some months of operation about a third of the American rural communities had no concept of the Marshall Plan, which certainly was keeping up the price of their products. These people are not dumb, they just have not become interested, and in these days of television, radio, two or three daily newspapers, a couple of weekly magazines and a few quarterly journals of opinion, the average American citizen has built up sales resistance; otherwise, he would be bankrupt. Our attempt to interest him in health education is confronted with a problem of breaking down this immunity. This not only goes for the public in general, but it goes for physicians in other fields of practice. Even here in the sessions of our American College of Allergists, we still have the job of attract-

ing the interest of our audience. You must be careful not to drive them away from concentrating on your paper by the use of strange words. Each of us allergists has a different perception mass and phrases and words mean different things to each of us. Be we nose and throat specialists, eye specialists, dermatologists, or pediatricians, our particular variety of shorthand language is so specialized that more than 75 per cent of our members cannot understand us if we use our own everyday medical dialect, so let's write briefly and so clearly that our own typist can understand what we are talking about. In fact, if she can't then you had better rewrite your paper, for it will be no good to present to any group of physicians even in your field of allergy. Once your paper has been written, boiled down to 1200 words and rewritten to your complete satisfaction, you are still not ready for the meeting.

If you stop to think about it, I am sure you will agree with me that to make a halting, stumbling, mumbling presentation is a positive insult to your colleagues. You are asking approximately 1,000 of America's leading physicians to spend ten minutes each or a collective period of 10,000 minutes while you present your thoughts, experiences and conclusions. This is something not to be undertaken lightly. You have an ethical responsibility.

So *use a timer as you practice reading your paper,* and you should practice reading it at least a dozen times or more until you are able to do it clearly, fluently and in exactly eight minutes with just the right emphasis on each word so it will convey its real meaning and have just the right value in relation to the other words on the page. You must do this even if it takes twenty-five rehearsals. The more you practice the more effective will be your presentation.

One more thing in this connection. *Remember you are going to have to speak into a microphone.* If you are microphone shy or if you are not experienced in their use, try to do your practicing in front of one. In any event, take your position far enough back of the mike to make yourself heard in all parts of the room without blasting the ears of your listeners.

If we all were to do these things, our meetings would continue to lead in interest and value and our attendance would continue to grow. If we fail to heed these suggestions, our meetings will tend to become dull and as deadly as most medical meetings, and our attendance will not be what it should be.

There is another thing that I would like to say to you who are younger than I—something that I would do myself were I to live my life over again—and that is the fact that *you can do research in your own practice and in your own laboratory.*

We allergists are often condemned by our colleagues, and by some who have set themselves up as arbitrators of our destiny; they say that we are not sufficiently productive. As a matter of fact, these persons who criticize us forget for the most part that we allergists have used up about all the biologicals scientists have been able to offer us for our use in the fields

of immunology (biological, chemical, physical) and from pathology (anatomical, physiological, and chemical) and related fields. In recent months, however, there has begun to flow a mass of new material from the basic scientists in physics and chemistry that can be and is being applied to immunology and pathology. These men, in turn, will in due course of time be sending to us material which we can apply to our patients, and new light will be shed on the nature of the allergic reaction and its management. Better days are coming!

In the meantime, I would urge that you dig in some place on some phase of investigation, especially you younger men not now connected with medical school faculties, before you take up stamp collecting, painting or specialize in golf—or should I say that golf is a sub-specialty? You should build a small laboratory in or near your home. Keep it out of your office, for it might run your patients out. In your home it can offer you as much fun and recreation as anything you can do, and in a short time you will be able to come to the annual meeting of the American College of Allergists, with a real contribution to its program and, therefore, to Allergy—maybe not an epoch-making, but certainly a definite contribution.

Shorter papers! Snappier papers! Understandable papers! Interesting and attractive papers presented in the best of reading English with charts and slides that do NOT distract, but preferably without either. I would urge that you put your charts, pictures and slides into an educational exhibit and give the men the benefit of a chance to study them.

If you come thus armed each year, your knowledge, your skills, your clinical judgment, and consequently your reputation, will all be so enhanced that you will be repaid a hundredfold for your effort. Just think what we shall make of our Society if as many as 10 per cent of our 1005 members will follow this suggestion. Our meetings would be terrific! Therefore, I would urge you to get busy, whether the other fellow does or does not.

Harold C. Hagen, M.C., representative in Congress, 9th District of Minnesota, presented a petition at the second session of the 81st Congress appearing in the Congressional Record, Vol. 96, No. 38, page 2346, which reads as follows:

"1903. By Mr. Hagen: Resolutions adopted by the American College of Allergists in opposition to any form of compulsory health insurance or any system of political medicine designed for national bureaucratic control; to the Committee on Interstate and Foreign Commerce."

AWARD OF VON PIRQUET MEDAL

President Jonathan Forman, when conferring the Von Pirquet Medal upon Dr. Paul Kallós, presented a brief biological sketch of the recipient:

Dr. Paul Kallós, a Swedish subject, was born in Budapest, Hungary, on December 14, 1902. After having studied and graduated (1920-1926) at the Elizabeth University of Péso, he received his degree of M.D. at the university. From 1924 to 1929, he was research associate and later head of the laboratory of the tuberculosis sanitarium, Baron Friedrich v. Korányi, at Budapest. From 1929 to 1930 he was research associate and clinical assistant at the Pediatric Clinic of the University of Leipzig, Germany. For two years following he was research associate and consulting physician for tuberculosis, internal medicine and diseases in allergy at the Dermatological Clinic of the City of Nürnberg, Germany, where he was in close collaboration with the famous dermatologist, Professor Ernest Nathan. The next year he did research work in Switzerland at the laboratories of the Tomarkin Foundation in Locarno, and the Institute for Research in Tuberculosis at Davos. He was also consulting physician for internal medicine and diseases in allergy at the sanitarium, Kurhaus Victoria, in Locarno, for one year. The next three years he was research associate and consulting physician for diseases of allergy at the Academic Hospital in Uppsala, Sweden, at the invitation of the Nobel-prize winner, Professor Robert Bárány. From 1937 to 1944 he was head of the immunological research laboratory of the Wenner-Gren Institute of Experimental Biology at the University of Stockholm. Since 1945 Doctor Kallós has been specializing in the practice of allergy and doing research in allergy at Helsingborg, Sweden.

JONATHAN FORMAN, M.D.

Dr. Paul Kallós is Editor of the book series, "Progress in Allergy—Fortschritte der Allergielehre," one of the Editors-in-Chief of the *International Archives of Allergy and Applied Immunology*, and Contributing Editor of the *Quarterly Review of Allergy and Applied Immunology*. He is an Honorary Fellow of the American College of Allergists and of the Argentina Allergy Society; Fellow, Founders Group and Executive Committee of the International Association of Allergists; Secretary, Southern Swedish Allergy Forum; Fellow, Swedish Association of Allergists, Swedish Association of Physicians (Svenska Läkarsällskapet), Medical Society at Lund, Medical Society at Uppsala, Swedish Association of Bacteriologists, Swedish Physiological Society, Scandinavian Association of Physiologists, and the Swedish Association for Internal Medicine.

Research grants have been awarded to Dr. Kallós by: Swedish National Association against Tuberculosis; King Gustaf V's Jubilaeumsfond; Lotten Bohman Foundation of the Caroline Institute, Stockholm, Hedstroms Minnesfond of the University of Uppsala; Swedish Medical Research Council; the Swedish Department for Public Health (Medicinalstyrelsen); and the American College of Allergists.

Dr. Kallós has published eighty-six papers covering his observations during this time.

PAUL KALLÓS, M.D.

Recipient of Von Pirquet Medal, 1950

SOME ASPECTS OF ALLERGY

PAUL KALLOS, M.D.

Mr. Chairman and Esteemed Colleagues:

It is with feelings of deep gratitude and devotion that I accept the great honor you have bestowed upon me, the von Pirquet Gold Medal.

In the word devotion is included my loyalty to the work of that great scientist Clemens von Pirquet and to those research workers and clinicians, who have already had this honor conferred upon them: Bela Schick, W. W. Duke, Arthur Coca, Robert Cooke and Milton J. Rosenau. When I think of the great pioneer work which these great workers have done, then I feel that you will permit me to use the word devotion. I am deeply grateful to receive this honor at a time when the American College of Allergists is being led by two such well-known men—not only as scientists but as great international organizers in our field—as Jonathan Forman and Fred W. Wittich.

At the request of Fred W. Wittich I am going to claim your indulgence by giving you my ideas on the allergical diseases. I will begin by saying that I cannot look upon allergical diseases as an isolated and strange group of disorders. My views, on the contrary, are that this group must find a place among all other diseases and that biological laws and features which are valid for all functions in living organisms must be valid also in this case.

I believe that it is too often forgotten that all the symptoms which we generally call "disease" are reactions of a living organism and not direct products of exogenous or endogenous noxious factors which cause them. Independent of the kind of the noxious agents all disease symptoms are expressions of functional or structural disturbances of the diseased organisms. This also means that the same symptoms, for instance fever, pain, disturbances of the circulation and of the volume, chemistry, and cytology of the blood, can be caused by many noxious factors. On the other hand, some noxious agents with special characteristics, such as bacteria or viruses, can in organisms of susceptible species cause reactions, with priority in certain organs. In this way specific diseases arise. Perhaps you will permit me to mention as one example poliomyelitis. If the virus of this disease can invade the central nervous system of an organism of a susceptible species, the metabolism of certain nerve cells will be disturbed and the cells themselves destroyed. This results in the paralysis of a number of muscles. The same virus cannot react with the nerve cells of other non-susceptible species and they therefore do not become paralyzed.

It was Clemens von Pirquet's and Bela Schick's great discovery which showed that the reaction capacity of a susceptible organism will be changed by a first contact with a noxious agent. This change of reactivity can cause a new contact with the same agent to result in reactions which are qualitatively and/or quantitatively different from the reactions shown in connection with the primary contact. The "disease" is the sum of the reactions of the organism to the effect of the noxious agent; therefore the change of the reaction capacity must result in a change of the picture of the disease. Von Pirquet further showed that this change of the capacity to react is a specific one, in other words, concerns only the noxious factor which caused the change. After the first contact the organism produces certain chemical bodies, called antibodies, which have a specific chemical affinity for and can react with the noxious agent which caused them. This reaction between specific antibody and noxious agent can result in a situation in which the functional and structural disturbances, that the noxious agent generally causes in the organism, become weakened or do not appear.

The antibodies affix themselves also to certain tissues. If the cells of these tissues get into contact with the noxious agent the antibody will react on the surface of the

cells with the agent. This chemical process is a stimulus for the cell, and the cell will answer with its normal function. A muscle cell will contract, a gland cell will produce secretion, a cell of the capillary wall will change its tonus and permeability, etc. The total sum of such reactions can also exceed the physiological limits and appear as a local or general disease. It is quite clear that the symptoms of this disease have no connection with the primary diseasing effect of the noxious agent, but instead they are characteristic for the specifically changed reaction capacity. This is to be understood from von Pirquet's very first work, his letter of April 2, 1903, to the Academy of Sciences at Vienna. He proposes for the changed capacity to react, the name "Allergy" and for noxious factors which can cause such a change, the name "Allergens."

The development of the allergic state can consequently result in weakening or abolishing the special diseasing effect of a noxious agent ("Immunity"), but the "allergic reactions" of antibody-containing cells can at the same time result in local or general disturbances of other kinds, which can reach the state of shock. In this way a close connection exists between immunity and allergy.

So far we have mentioned only noxious agents, that is factors which under certain conditions have a diseasing capacity in the great majority of individuals of a certain species. Von Pirquet has in the serum sickness discovered a disease which is not caused by a noxious factor in this meaning. Blood serum from animals of different species is not harmful or noxious in itself; it is tolerated even in large quantities without reactions which exceed the physiological limits. After a first contact with such a serum the capacity to react becomes changed; the organism becomes allergic; antibodies will be developed and affixed to certain tissues. A second dose of the same kind of serum brings it into contact with these cells and they react, with local or general disease symptoms as the final result. Serum sickness has consequently the same mechanism as the anaphylactic state of experimental animals, dicovered by the famous French physiologist Charles Richet and his school, also at the beginning of this century.

In anaphylactic experiments and in the serum sickness the primary contact with the allergen is deliberately produced by a third person. The clear-cut presentation of the American physiologist S. Meltzer (1910), very well known to you all, gave us the conception that the human sickness asthma bronchiale has the same mechanism as the anaphylactic state in experimental animals. We very rightly assume from this the beginning of the clinical science of allergic diseases.

In the case of asthma and certain other diseases, for instance urticaria and eczema (Eli Maschowitz, 1911), the cause of the incapacitating reactions is substances in the environment, which are absolutely inert in the great majority of individuals of the same species. A primary contact with some kind of such allergens (for instance pollens, molds, foods, dust, animal danders, etc.) produces in certain individuals with hereditary disposition an allergic state. This primary contact is established by chance. Antibodies will be produced and affixed to the tissues, and after this every new contact with the specific allergen results in stimulation of antibody-containing cells and consequently in disease. The localization of the antibodies in various tissues or organs, the way in which the allergen reaches the allergic organism, and the quantity of the allergen are the deciding factors as to the kind of resulting symptoms. In these cases the development of antibodies has no useful function; the allergens are certainly no "noxious agents." In 1937 we had proposed the hypothesis that the development of antibodies against innoxious agents is an inherited functional fault. The heredity of disposition to be allergic is proved by A. Coca, A. S. Wiener and others. Not only human beings but also animals can have such a disposition and become allergic, as shown in the important research work of F. W. Wittich.

In this discussion I have not mentioned the fact that living noxious agents, such as bacteria and viruses, have a reproducing capacity and often also produce harmful sub-

stances (toxins). The invasion of a susceptible organism at a given moment by a number of microörganisms is consequently no endpoint; on the contrary it represents the beginning of a combat, in which the enemy, the invading microbes, sometimes increase in number, invade various organs and disturb their structure and function; the toxins paralyze other functions. The picture of disease so resulting is perhaps dominated by these phonomena. The organism develops antibodies and reacts in many other ways against the harmful effects of the microörganisms. If these reactive processes can prevent the further reproduction of microörganisms and stop the attack or at least localize it to certain limited areas, we get the opportunity of showing the reactions of the organism in a clearer manner.

Allergic diseases *sensu strictiori* are caused by allergens which in themselves are not harmful. As is shown, the production of antibodies against allergens of this kind, antibodies without useful function, leads to reactions of the allergic organism which are out of proportion to the severity of the attack. Thus the allergic state is often called "hypersensitivity," a name which has no real foundation and should be avoided.

The only important fact which concerns us here is that the allergic organism, through its changed capacity to react, can sometimes respond with identical reactions to different kinds of allergens, for instance to living pathogenic microörganisms on the one hand and to innoxious agents on the other. Thus it is not surprising that the same clinical picture can sometimes be produced by living microörganisms as well as by simple allergens, bearing in mind such disorders as "rheumatic" manifestations, nephritis, periarteritis nodosa, etc.

Every stimulation of cells leads not only to direct reactions but also to reactions in other cells as response to the altered functional state and sometimes also to the condition caused by substances, so-called mediators, such as histamine, sympathine, acetylcholine, etc., released from the stimulated cell. In this way a local stimulation will lead to a general reaction of the whole organism. On the one hand the functional disurbances spread, and on the other regulative and reparative processes start.

The first contact with an allergen starts in a susceptible organism a special disturbance in the globuline synthesis. Instead of normal serum gamma-globulines being produced, globulines are produced with altered structure, such as specific antibodies. If the globulin-producing cells have developed some kind of antibodies, then they retain the capacity of so doing even after the elimination of the allergen. In this state every stimulation of these cells can cause a renewed production of antibodies ("anamnestic reaction"). In this way an allergic state can remain for a long period even when contact with the specific allergen is prevented.

Not only have the protein-producing cells such a "memory," but the whole organism has. If an allergic organism has reacted several times to the specific allergen in a special way, for instance by urticaria to eggs, by rhinitis or asthma to pollens, etc., the kind of reaction can be a sort of "conditioned reflex." In this state the reaction, the "allergic disease," can be started not only by the allergen but also by many other influences, and last and certainly not least by psychic ones.

I have tried here to show only some fragments of the tremendous allergic mosaic and how it appears to me. It is worth noting that our prophylactic and therapeutic measures are directed by the knowledge of the sketched biologic processes. If possible we will prevent the development of allergy in persons with known hereditary disposition; we will in every case try to ascertain the allergens and eliminate them from the environment of the allergic. If an allergic disease is already established, we try to interrupt the chain of reactions, the entirety of which is the disease. Remedies here come to play their part. As W. Hughes (1946) wrote, any remedy which would inhibit the reactivity of the organism without doing harm should cure every "allergic" disease. We are short of such remedies. Perhaps "Cortisone" and ACTH promise something in that direction. All the other remedies only interrupt the chain at some

special points and give only symptomatic relief. The organism retains the antibodies and also the capacity to react afresh.

The animal experiments of Ch. Richet, Milton J. Rosenau, and A. Coca and the clinical experience of L. Noon, J. Freeman, R. Cooke, W. W. Duke and others showed that repeated injections of the specific allergen can bring about a state in which the allergen will be tolerated by the allergic organism without disturbances. R. Cooke and his school discovered that this treatment, called "hyposensitization," leads to the development of a new kind of antibodies, which do not affix to tissue cells and consequently can react with the allergen without stimulating the cells. The latest results of A. S. Wiener confirm these findings. We are engaged in serological investigations which will enlighten us as to the role of the different kinds of antibodies in the course of the allergic state. I feel that hyposensitization is the most promising therapy at the moment. In my experience it has given about 70 per cent beneficial results.

Much has been done and there is very much left for all of us throughout the world to do. We must work together for this end, and I at this solemn moment, deeply conscious and grateful to you for this great honor, do promise that I will still further devote myself to this great task and look forward to the day when we can meet in person in a peaceful world and refortify ourselves for the work which is still to be done. I thank you all.

THE AMERICAN COLLEGE OF ALLERGISTS

Proceedings of Sixth Annual Meeting

The Sixth Annual Meeting of The American College of Allergists was held at the New Hotel Jefferson, St. Louis, Missouri, January 15-18, 1950. Publication of the program of this meeting is intentionally omitted from the ANNALS, since all members received copies earlier, and because it is necessary to conserve space for an accumulated backlog of manuscripts. Any member desiring an extra copy may have the same upon request.

Owing to unforeseen difficulties and conflicting allergy meetings, it was necessary, in order to secure technical exhibitors, to advance the program somewhat, so that only nine months had elapsed since the Fifth Annual Meeting held at the Palmer House in Chicago. Because of this rather short interval of time the Program Committee experienced some difficulty in securing worthwhile papers, and thus found it impossible to prepare the program bulletins and place them in the mails as long a time in advance of the date of the meeting as it would otherwise have done.

About sixty members who had actually made hotel reservations and planned to attend the St. Louis Meeting found it impossible to be there. Some of these had plane reservations, but could not get off the ground because of poor flying conditions; others who had rail transportation were handicapped by the unusual floods resulting in disorganized train schedules.

Thirty-three technical exhibitors were present and exhibited products related to allergy. Included in this number were the majority of our Sustaining Members. The highlight of the Scientific Exhibits was the three-booth display allotted to ACTH, ACE and Cortisone in Allergy, by Drs. Theron G. Randolph, John P. Rollins, and Michael Zeller.

The two simultaneously conducted scientific programs were a complete success, due very largely to the fact that the more representative allergists in the College were present. Among the highlights of the Session were the Panel on Itching Dermatoses on Tuesday, January 17, at 2 p.m.; the splendid address by our guest speaker, Doctor

Vera Walker, President of the British Association of Allergists, of London, England; and the presentation of the Von Pirquet Medal, *in absentia,* to Dr. Paul Kallós of Sweden. All in all the program was an excellent one, largely owing to the untiring efforts of the Program Committee, of which Dr. Sim Hulsey was chairman. Much credit is also due to Dr. Jonathan Forman, who personally handled all the advance publicity for the meeting and whose inspired leadership alone would have assured its success.

A most successful cocktail party in the Gold Room on Monday evening served as a medium for promoting good fellowship. Since the majority of the members had made plans for, and had expressed a preference for, private dinners and entertainment, it was decided to dispense with the customary annual banquet this year and in succeeding years. A spirit of great cordiality and enthusiasm was everywhere in evidence throughout the entire meeting.

Next Annual Meeting

By unanimous action it was decided to hold the next annual meeting of the College at the Edgewater Beach Hotel in Chicago, February 11-14, 1951. It will be preceded (February 9-11) by a three-day intensive Graduate Instructional Course in Allergy. Dr. Albert V. Stoesser, Chairman of the Program Committee, and his associates, President John Mitchell and Secretary-Treasurer Fred Wittich, have already arranged the schedule for the Instructional Course, which is to be made available to all registrants attending the College Session; and the committee promises that it will feature many innovations.

Registration will begin on Sunday, February 11, at 2 p.m., and will not in any way interfere with attendance at the Instructional Course. There will be no Technical or Scientific Exhibits on Sunday. These will be featured on Monday, Tuesday, and Wednesday, February 12, 13, and 14. A Scientific Program will also be held on these same days.

Brief Résumé of Business Transacted

The Secretary-Treasurer reported a total membership of 1,005, including all classes. Two members were advanced to Active Fellowship, making a total of six so advanced during the past year. The list includes Thomas W. Collier, M.D., Captain Ross Imburgio, M.D., John F. Kelly, M.D., William H. Lipman, M.D., Ronald V. Silknetter, M.D., and A. Harvey Simmons, M.D. Hereafter the Secretary-Treasurer will make a survey of members preceding the annual meeting to determine which warrant promotion to Active Fellowship, and the list so submitted by him will then be acted upon.

During 1949 the College sustained, through death, the loss of the following members: W. Byron Black, M.D., and Arthur Kalisch, M.D. Obituaries appeared in the ANNALS OF ALLERGY, and condolences were sent to the families.

At the general business meeting held on Tuesday, January 17, the following officers were elected to serve during the ensuing year and until their successors are duly elected and qualified:

Officers

President-Elect—Harold A. Abramson, M.D.
First Vice-President—Theron G. Randolph, M.D.
Second Vice-President—Susan C. Dees, M.D.
Secretary-Treasurer—Fred W. Wittich, M.D.
Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.

Board of Regents

One-Year Term	*Two-Year Term*	*Three-Year Term*
Harold A. Abramson, M.D.	Hugh Kuhn, M.D.	L. O. Dutton, M.D.
Robert F. Hughes, M.D.	John D. Gillaspie, M.D.	Norman W. Clein, M.D.
Boen Swinny, M.D.	Herbert Rinkel, M.D.	Stephan Epstein, M.D.

Doctor Wittich presented a complete financial report covering the ANNALS OF ALLERGY for the year ending November 30, 1949, reflecting a total profit of $7,082.53 as compared to $6,868.38 for the preceding year. Fifty per cent of this amount goes to the College.

Mr. Eloi Bauers, Counsel for the College, discussed the legal aspects of, and the questions involved in, the renewal of the contract with the Bruce Publishing Company for publication of the ANNALS, and upon his recommendation it was decided to continue the same in force for a period of three years from last November, 1949.

The Finance Committee report, given by Dr. Boen Swinny, showed an operating profit of $4,631.29 for the calendar year 1949, as compared with an operating loss of $1,136.54 for the preceding calendar year. Upon recommendation of this committee, it was decided that hereafter the publication of panel discussions, such as "Psychodynamics and the Allergic Patient," will not be supported by the College because of the extra work it places on the staff and because the work and time involved are out of all proportion to the profits realized therefrom, and that in the future the College will confine itself, so far as publications are concerned, solely to the ANNALS OF ALLERGY. All authors will be requested to furnish the College with translations of manuscripts. Letters addressed to the College will, of course, continue to be translated at College expense.

The committee recorded its opposition to the use, in future years, of funds obtained from initiation fees for the purpose of helping to defray current expenses. It feels that the ultimate objective of the College should be the payment of all operating expenses solely from the income received from membership dues collected, plus such revenue and profit as may result from instructional courses, which, it was decided, will hereafter be held in connection with, and immediately preceding, annual meetings. These courses are to be geared to the student interested in allergy, and instructors will be expected to pay their own expenses, since they will be attending the annual meeting of the College at the same time.

The committee decided not to set up a proposed budget for the current year's expenses, but rather to recommend that expenditures, in 1950, in each category enumerated in the current audit report be limited, as far as possible, to the amount actually spent for such items during 1949.

By appropriate and unanimous action the annual dues for both Active and Associate Fellows were increased by the sum of $5.00.

Action was taken to set up a Pediatric Committee with Dr. Bret Ratner as chairman, for the purpose of stimulating interest in pediatric allergy, with authorization to the committee to set up a morning program on pediatrics at the Edgewater Beach Session in February, 1951.

The College placed itself on record as opposing any form of compulsory health insurance or any system designed for national bureaucratic or political control of medicine, and copies of this resolution have gone forth, not only to the President of the United States, but also to many members of Congress. These latter were respectfully asked to use every influence at their command to prevent the enactment of such legislation.

Doctor Wittich reported on a survey of various medical societies which he was instructed to make for the purpose of developing a section on allergy under the auspices of the College. He reported to the Board that six state societies, including New Jersey and Louisiana, are now offering well-rounded programs in allergy. The New Jersey section meets every other year. Florida and Connecticut have state allergy societies which meet on the day immediately preceding the meeting of their state medical societies. Minnesota will establish a section in 1950 under the auspices of the College. Eighteen societies replied that they were referring the resolution to the proper committee. Five of those replying stated that they were not interested be-

cause of an insufficient number of doctors in their respective areas, and because they did not have separate sections of any kind in the meetings of their respective state medical societies.

Authority was given Dr. Harold Abramson to arrange for a course to be known as "Psychotherapy for Allergists," to be given under the auspices of the College by Dr. Sandor Rado, at Columbia University in New York City, November 6-10, 1950.

The Committee on Rheumatism and Arthritis was authorized to continue its research work as funds are made available for the purpose, all such appropriations to be kept under the supervision of the Secretary-Treasurer and to be credited to "research funds."

It was also decided that as the Committee on New and Unused Therapeutics makes further detailed studies of new drugs, such studies will from time to time be published in the ANNALS OF ALLERGY. A booklet will also be prepared on basic dust-elimination precautions, to be printed and put on sale, or distributed through members of the College and others.

The Pollen Committee stressed the need for more standardization on the collecting, handling, labeling, and storing of dry pollen.

A resolution was adopted amending the By-Laws so as to provide for the creation of the office of Assistant Secretary-Treasurer, and such other additional offices as the Board from time to time may designate and fix. Dr. Albert V. Stoesser was thereafter elected Assistant Secretary-Treasurer.

The Nominating Committee, after extensive discussion and consideration, presented the following official slate of officers to be voted upon in 1951.

Officers

President-Elect—J. Warrick Thomas, M.D.
First Vice-President—G. Estrada de la Riva, M.D.
Second Vice-President—L. Dell Henry, M.D.
Secretary-Treasurer—Fred W. Wittich, M.D.
Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.

Board of Regents for a Three-Year Term

Bret Ratner, M.D.
Hyman Miller, M.D.
Walker L. Rucks, M.D.

It was decided, in view of the changes made in the several By-Laws at this meeting, as well as numerous other changes and amendments made during the past several years, that the corrected By-Laws, additions and amendments to date be arranged and published in booklet form, and that after the printing proofs have been prepared they be sent to all members of the Board and to the Editor of the ANNALS for any final corrections before publication, after which they are to be returned to Mr. Bauers for final study and then on to the Secretary-Treasurer who will arrange for the printing.

Dr. M. Murray Peshkin reported on the progress made toward certification in allergy by the American Society of Certified Allergists, and was given a vote of continued confidence and appreciation for his untiring efforts.

Progress in Allergy

ANTIHISTAMINIC AGENTS

A Review

ETHAN ALLAN BROWN, M.D., F.A.C.A.
WILFRED KRABEK, M.S.
Boston, Massachusetts

HISTORICAL SURVEY

The work of Dale and Laidlaw in 1910,[1] of Dale in 1920[2] and 1929[3] and others has provided evidence in favor of the now quite generally accepted theory that anaphylaxis is due to the combination of antigen with antibody within the cells of the body, which are thereby damaged. The resulting symptoms may be due, in part, to this damage and in part to the release of histamine, histamine-like substances and other substances of which heparin is probably one.

In 1910[4] and 1911,[5] Barger and Dale showed that histamine was present in naturally occurring materials, i.e., in ergot and intestinal mucosa. In 1927, Best, Dale, Dudley and Thorpe[6] suggested that histamine was liberated from the tissues of the animal body by cell stimulation, due to the inter-action of antigen and antibody. In 1931, Watanabe[7,8] demonstrated that the lungs of guinea pigs, and the livers of dogs were considerably reduced in their histamine content after anaphylactic shock.

Dragstedt and Gebauer-Fuelnegg[9] in 1932 reported the presence of a histamine-like substance in the blood and lymph of a dog during anaphylactic shock. In 1936, Dragstedt and Mead[10] showed that the amounts of histamine in the inferior vena cava blood above the diaphragm in the anaphylactic dog were very similar to those required to produce the same changes by intravenous injection.

In 1927, Lewis[11] described the triple response of the skin to histamine and pointed out its resemblance to allergic urticaria and to the effects of various other forms of injury.

Lewis and Grant[12] in 1926 compared the reaction of histamine and fish extract in a fish-sensitive patient and found that when histamine and the fish extract were punctured simultaneously into the patient's skin, the resulting reactions were identical.

Hare[13] examined a pollen-sensitive and two horse-sensitive patients and found that pollen extracts and horse extracts also produced the three-fold skin reaction of Lewis.

In a child suffering from cold allergy Bray[14] observed that the triple response of Lewis resulted when the patient immersed his hands in water at 45 degrees F, indicating that while the physical allergies were presumably not immunological in nature they might be mediated, at least in part, by histamine or a histamine-like factor.

Horton, Brown and Roth in 1926[15] and Rose in 1941[16] found a slight increase in blood-histamine after skin stimulation in cases of dermographism. In this respect it should be noted that while various local effects may be due to the release of histamine, the quantities released may be insufficient to be detectable in the blood and the amounts that reach the blood stream are normally quickly removed. Also, there is a wide range of sensitivity to histamine in different individuals, both allergic or non-allergic.

To summarize, histamine (or histamine-like substances) appears to be present in small amounts in practically all tissues, either as a progenitor, in a combined form, or possibly free in extremely small amounts. It possibly acts as a mediator or

Dr. Brown is physician-in-chief, Allergy Clinic, Boston Dispensary, Boston, Mass., and director, Asthma Research Foundation Inc., Boston, Mass.

regulator for physiological processes and under certain circumstances, it appears to result in certain pathological states.

Among the considerable number of reviews on histamine, its derivatives and its pharmacological action, are those of Feldberg and Schilf in 1930,[17] Guggenheim in 1940,[18] Dragstedt in 1941,[19] Feldberg in 1941,[20] Rocha e Silva in 1942,[21] Code in 1944,[22] Selle in 1946[23] and Rose in 1947.[24]

In view of the increasing evidence of the important role that histamine appears to play an allergic phenomena, it is natural that any evidence of antihistaminic action of drugs would immediately be utilized. Many drugs, such as epinephrine, atropine, papaverine and other sympathomimetic substances, antagonize the action of histamine through their antagonistic effect on the tissues involved. They are, however, relatively non-specific for histamine-mediated conditions. They frequently affect only one or a few phases of the allergic reaction.

The usefulness of histaminase as an antihistamine is controversial. Feinberg in 1946[25] was of the opinion that it lacked any specific effect in allergic conditions.

It is not the purpose of this paper to discuss the relatively non-specific drugs, but to review briefly what are commonly called the "antihistaminic" drugs. Histamine antagonists of antihistamine agents have been ably defined by Loew[26] as "drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and which do so by a mechanism other than the production of pharmacologic responses diametrically opposed to those produced by histamine. True antihistaminic agents are able to antagonize histamine without eliciting pharmacologic responses, or if responses are elicited, they do not appear to be of the type or degree which suggest an important causal relationship to the histamine antagonism." In this paper those drugs will be considered which, from the available evidence, appear to block the action of histamine with some degree of specificity; which are relatively non-toxic to humans and are, for the most part, available commercially either as "new drugs" or as drugs which have undergone relatively extensive clinical trial. This eliminates agents such as atropine, epinephrine and the like, the effectiveness of which in antagonizing other spasmogenic agents of different physiologic types is frequently greater than their effect on histamine-induced conditions.

A number of excellent reviews have been published on various aspects of the antihistamine drugs. These reviews include those of Loew[26] on their pharmacology, Huttrer[27,28] on their chemistry and pharmacology, Hunter and Dunlop[29] on their pharmacological aspects, Feinberg[25] and Haley[30] on their clinical uses.

The rationale of the use of the antihistaminic agents rests on two theories: (1) that symptoms of anaphylactic shock are due, in part at least, to a liberation of histamine, and (2) that allergic disease in man is the counterpart of anaphylaxis.

A more or less quantitative correlation appears to exist between a given amount of histamine and the more effective of the antihistaminic drugs. It is upon this relation that the use of the term antihistaminic is justified. Huttrer considers that in order to be considered specifically as an antihistaminic, activity at least of the order of 1-10 *μμg./ml.* of bath liquids should counteract the contracting effect of 1 *μμg./ml.* of histamine as tested on the isolated guinea pig small intestine. Other tests as to protection against histamine-produced symptoms must also be satisfied.

In animal tests and in clinical experience, it has been found that the antihistaminics do not counteract all of the pharmacological properties of histamine. This may be due to a number of reasons. The antihistamine drugs may act through adsorption or other combination with histamine receptors, thus directly blocking off the histamine. This would explain the action, in some cases, of the antihistaminic moderating histamine activity to a greater extent when introduced into the tissues before the histamine, than when applied simultaneously or afterward. Under other circumstances, the reverse may be true. Histamine evidently has a number of receptors, presumably many of them different from each other. Therefore, if the anti-

histaminic drug acts by virtue of the similarity of its structure to histamine, as there is some evidence that it does, a consideration of the stereochemical relationships would lead to a possible explanation as to why some antihistamine compounds vary in both type and degree of activity. Spatial relationships may permit ready combination with some of the histamine receptors and little or none with others. The relatively high (240 and up) molecular weight of the more effective histamine antagonists would seem to bear this out.

The size and shape of the groups at the ends of the key grouping quite possibly determine the degree of blocking of the histamine as well as the ability of the antihistaminic molecule to replace the histamine already in contact with its receptors.

Another factor which may be considered is the so-called intrinsic and extrinsic histamine. If the histamine is released, whatever the mechanism, in close proximity to the histamine receptors there is certain to be less opportunity for a foreign substance (the antihistaminic agent) to counteract it than if the histamine is released in one place and has to travel by the humoral system to the location of its receptors. In this case, the permeability of the cell membrane to the antihistaminic substance may well play a part, particularly since some of the antihistaminic drugs are said to be surface active. Factors that may affect the application of the antihistamine drugs include solubility, degree of hydrolysis, which in turn may affect the solubility or absorption, and the rate of absorption of the compound. Lack of activity on the part of the antihistaminic obviously might be due to a number of factors in addition to those just stated. Among these are the possibility or even the probability that histamine has a number of quite widely different types of receptors resulting in widely different symptoms. Some of these receptors may not correspond to a sufficient extent with the spatial relationship of a given antihistaminic, resulting in a lack of favorable activity on the part of the latter. It may also be possible that some of the symptoms ascribed to histamine are either not due to histamine or are due to the combined action of histamine with another pharmacological agent, as for example, acetylcholine.

The antihistaminic agents are frequently classified as derivatives of ethanolamine (Benadryl) or ethylenediamine (Antergan). A somewhat more basic unit so far as functional structure is concerned would seem to be that of the ethylamine skeleton. Essentially all of the compounds which have to a considerable degree at least, a relatively specific antihistaminic action, contain this group. It may be in the form of a "straight chain" compound such as Antergan or as part of a ring compound such as Antistine. If this group is taken as basic, then such widely different (structurally) compounds as Thephorin, Antistine, Perazil, Trimeton and Phenergan, as well as most, if not all, of the other antihistaminics, that have shown sufficient promise to reach the commercial stage, show a common factor. This is not true if ethanolamine or ethylenediamine are taken as basic units, even though they may be the actual starting point for the synthesis of the compounds. This ethylamine skeleton also corresponds to the side chain of the histamine molecule and to part of the imidazole chain.

A correlation of the extensive published literature on the antihistaminic compounds arranged according to groups attached to the basic unit, with the apparent degree of antihistaminic activity, the effect on various allergic symptoms and side effects should prove interesting and might well lead to new lines of investigation. Work in this direction has been done to a varying degree in a number of papers,[26,27,30,31,32,33] particularly in regard to direct antihistaminic activity.

Apparently the terminal nitrogen should be a tertiary nitrogen (Kohler[34]) to attain significant antihistamine activity although it may be part of a heterocycle as in Linadryl or Pyrrolazote. Methyl groups on a terminal nitrogen appear to result in a less toxic product than ethyl groups. The same appears to be true when the

methyl groups are part of a ring structure such as Perazil and Linadryl. Other energy factors probably play a part in these cases.

Ether linkages on the carbon of the basic ethylamine skeleton appear in general to lead to more toxic products (929 F and Benadryl), although the groups attached to the ether oxygen have a definite modifying action. For example, Benadryl is much less toxic as well as less active than 929 F and Decapryn appears to be less toxic than Benadryl. In Benadryl, the thymol group of 929 F has been replaced by the benzhydryl group. In Decapryn, one of the phenyl groups of Benadryl has been replaced by an alpha pyridyl. Use of beta or gamma pyridyl instead of alpha pyridyl, at least in the Pyribenzamine series leads to a decrease in activity.[35] Replacement of a benzyl group by a thenyl[36] or a halogenated thenyl group [37] leaves essentially the same activity.

Among some of the newer compounds of a different structure are the thiophene derivatives such as Pyrrolazote, Phenergan, 3356 RP, and the pyridindene (or indenopyridine) derivatives as for example, Thephorin. In the case of Thephorin the basic unit is included entirely in the pyridine ring.

The antihistaminic effects of various compounds are evaluated in a number of ways. One of the difficulties in evaluating results from different laboratories is the variation in techniques, frequently omitting the necessary data for, at least, an indirect comparison. Briefly, the following methods are in use: (1) inhibition of the histamine-induced contraction of isolated guinea pig intestinal strip by prior application of the antihistaminic; (2) relaxation of the intestinal strip by application of the antihistamine after the contraction has taken place; (3) counteracting the contraction of a tracheal chain made from the trachea of a guinea pig; (4) prevention of histamine poisoning in the guinea pig due to subjection to aerosolized histamine; (5) prevention or alleviation of histamine intoxication caused by one of several methods of application, for example intraperitoneally, depending upon the type of reaction it is desired to observe. In the clinical evaluation of the antihistaminic agents the results must be considered with care. Many of the tests do not have adequate controls. In some cases the apparent alleviation with placebos alone may run as high as 33 per cent.

Some of the antihistaminic agents show unexpected activities. Brewster and Dick[38] found that Benadryl had a significant bacteriostatic activity. They found that the blood reached inhibitory levels after treatment for twenty-four hours at the rate of 50 mg. every four hours. In connection with this must be considered the observation of Halpern and Reber.[39] They found that 80 per cent of the animals infected by subcutaneous injection of Salmonella typhimurium or staphylococcus and then treated with an unspecified amount of Phenergan, developed septicemia and died. Controls similarly infected, but not treated with the drug, survived. It is assumed that the drug, in preventing the edema, destroyed a natural barrier to the diffusion of the infection in the body.

Pellerat (cited by Huttrer[28]) has given a possible explanation of so-called histaminoid accidents which may be associated with the use of antihistamines. He suggests that histamine released by the antihistaminic agent from receptors which have a preferential affinity for the antihistaminic agent may be set free and travel by the humoral system to another group of receptors which are inadequately protected, either by an insufficient amount of antihistamine or by a lesser affinity for it than for histamine, thus setting up a remote reaction. Since the more powerful the antihistaminic agent the more it is taken up by the tissue, Pellerat suggested that more histaminoid accidents might be expected with the availability of powerful antihistaminic agents.

The antihistaminic agents were found by Winter[40] to have a potentiating effect on the sedative action of barbiturates, hence the ingestion of barbiturates with antihistamines must be used with caution.

Dreyer[41] has summarized some of the activities of the antihistamine drugs essentially as follows: Some "possess local anesthetic properties, they have atropine-like, antispasmodic, quinidine-like, demerol-like and musculotropic actions, . . . some antihistamines sensitize to epinephrine while others desensitize. The antihistamines have dual actions on some tissues as shown by their effects on striated muscle. In small concentrations, there is increased contraction due to indirect (nerve) stimulation. In high concentrations, indirect stimulation is suppressed, presumably because of block at the myoneural junction but contraction is not inhibited upon direct stimulation of the muscle. Similarly, the antihistamines depress impulse transmission at autonomic ganglia. In the autonomic system, cholinergic responses are partially or completely depressed, depending upon the drug used, whereas adrenergic responses are usually undiminished and may even be potentiated by some drugs." Some drugs "in small doses depress intestinal motility but in large doses they stimulate. Other drugs stimulate motility in small doses but depress in large doses."

CLINICAL REVIEW

In any review of the antihistaminic drugs, one very important consideration must constantly be kept in mind. There are, at present, no means by which the effects of such agents can be measured with any accuracy in man. The papers, which deal with clinical evaluation, concern data which cannot be reproduced excepting within very wide limits. The environment, as regards inhalants, pollens and moulds, changes continuously. In addition to symptomatic treatment, the patients frequently receive both injection and psychotherapy. No two environments or seasons, no two patient populations are identical. The method of clinical evaluation varies with each physician who has his own interpretation of the patient's necessarily subjective report. One patient may complain bitterly because he has thirty minutes of symptoms each morning, while another considers himself blessed because his symptoms are limited to only half an hour.

The toxic effects in animals vary greatly from those seen in man and there has so far been no predictable correlation between the effects in the experimental animal and in human beings. In any case, the effects are multiple and the good results seen may as often be due, as for instance, to sedation in Benadryl, as to stimulation as seen in Neohetramine, as well as to other effects not directly related to those antihistaminic in nature. Without exception, all of the histaminalytic drugs cause side reactions. No regularity of pattern response is known, although millions of doses have been administered. A drug, which causes severe side reactions in one patient, may be taken by another with no ill effects. Another drug, of supposedly lower toxicity, may cause unbelievably severe untoward reactions in a susceptible individual. In some patients, such reactions may be caused by two drugs of dissimilar origin, while in others, another drug of similar but not identical chemical structure can be taken with impunity.

The antihistaminic agents are inconsistent in their action, in that a drug may be effective at one time for a patient and not for a second administration, although the patient's condition may appear to be the same. Ineffectiveness is also capricious. In occasional patients, prolonged administration of a drug which causes side reactions may lessen them, while in others, each successive dose brings on more severe side reactions until the patient is completely intolerant of even the smallest dose. There is no predictable method of deciding whether the patient will benefit from any one drug, although it is usually the rule to administer the drug which is either known to have the smallest percentage of side reactions, or the greatest degree of efficacy.

All of the following reactions have been listed in the literature and the greater number of these are undoubtedly authentic. Others, limited to one drug, will be described in the course of the review. By far, neuropsychiatric reactions are most common. They include drowsiness, dizziness, faintness and fainting attacks, mental

confusion, incoordination, disorientation, stupor, narcolepsy, coma, giddiness, general hallucinations, apprehension, nervousness, weakness, fatigue, light-headedness, headache, amnesia, lassitude, choked speech, slurred speech, somnambulism, a sense of exhaustion, irritability, athetoid movements, spastic jactations, acute melancholia, suicidal tendencies, bilateral tinnitus, peripheral neuritis, insomnia, tremor, a sense of relaxation, mental lethargy, "walking on air," acute hysteria, jerky and rapid speech, and "an all gone feeling in the pit of the stomach," as well as generalized numbness.

In the ophthalmic system, the patient may complain of photophobia, dimming of vision, dilated pupils, rapid nystagmus, difficulty in accommodation, blurring of vision, and visual hallucinations. Other side reactions include muscular aching and twitching, low back pain and genito-urinary symptoms as impotence, incontinence, bladder discomfort and frequency.

In the respiratory, alimentary and cardiovascular systems, the patient may complain of a dry nose, dry oral cavity, a bad taste, chloroform-like taste, olfactory hallucinations, epigastric distress, nausea, vomiting, indigestion, pyrosis, sore tongue, abdominal cramps, constipation or diarrhea. In some patients, indigestion has caused bronchial asthma and, in others, respiratory arrest requiring artificial respiration. There may be complaints of excessive perspiration, cold extremities, digital vasospasm, hot flashes, shock-like reactions and chills, as well as orthostatic hypotension, true hypotension, palpitations, elevated pulse rate, a tendency to bleeding and facial edema.

In the skin, an aggravation of the original symptoms may be seen, as well as urticaria and generalized pruritus, eczematoid dermatitis, pityriasis-rosacea-like reactions and erythematopapular eruptions.

Since patients who take the antihistaminic drugs may be the subject of study for other conditions, it is important to note such effects which the drugs do not appear to possess. Of these, Benadryl has been the best studied, and it has been demonstrated to be without effect on the basal metabolic rate or the body weight, although other antihistaminic drugs lower the basal metabolism. Taken orally, it does not affect the eye, in which topically applied 0.5 per cent solutions cause moderate dilatation, while stronger solutions cause accommodation interference. Doses up to 300 mg. effect no change in the pulse rate or the electrocardiogram, although systolic blood pressure may be lowered. Occasionally, severe hypertension may occur. The urine is unchanged for its constituents, volume, the urea nitrogen or the non-protein nitrogen. Dilution and concentration tests remain within normal limits. Circulation time is unchanged. Blood chemistry and blood constituents remain normal, although granulocytopenia may appear. Benadryl is reported as increasing gastric acidity in the young and decreasing it in the elderly, although following stimulation with histamine. In doses up to 400 mg. Benadryl has no effect upon the glucose-tolerance curve, although doses of 30 mg. intravenously may increase the glucose-tolerance, while decreasing the body temperature approximately 1 degree F.

The wheal following intradermal histamine is decreased, but the wheal resulting from the injection of trypsin, horse serum or staphylococcal toxin in sensitized animals is not affected. The development of the Arthus-type of reaction following horse serum injection is not prevented by either Benadryl or Pyribenzamine.

ANTERGAN

In an epoch-making communication which appeared in December of 1942, Halpern[42] described two Rhone-Poulenc compounds 2325 and 2339 (Antergan) as representative of a new class of substitute polymethylene diamines, which were extremely active against the asthma induced by histamine. The author stated that since the new compounds were only weak spasmolytic agents, their antagonism to histamine was due to specific inhibition of the stimulating action of histamine on the bronchial muscles. The minimum protective dose of 2339 RP was 1 mg./kg. in guinea pigs. The LD_{50} was 175 mg./kg. and 5 mg. of 2339 RP per kg. completely protected the

animals against 40 lethal doses of histamine. In the dog, the compound prevented the appearance of anaphylactic shock as marked by hypotension and hemoconcentration. Oral administration required ten times the parenteral dose to show prophylactic action. It was considered that the ineffectiveness by the oral route might be due to delayed gastrointestinal absorption, since the protective action was not evident until forty to fifty minutes after ingestion and histamine antagonism was still evident six to eight hours afterwards.

In an attempt to discover the influence of synthetic antihistamines on antibodies seen in anaphylactic shock, Halpern[43] later sensitized rabbits with intravenous injections of suspended lamb erythrocytes diluted 1:10 and then gave them anaphylactic doses of 2, 3 or 5 c.c. of the same antigen. Three of the seven rabbits were protected by 40 mg./kg. of Antergan, but all seven died immediately or within two hours. The antibodies measured in blood samples collected five minutes after the injection of the antigen did not fall appreciably. Any slight decline noticed was attributable to previous sampling. Halpern concluded that this method was unsatisfactory for studying the effects of antihistaminics on antibody formation because the sensitization itself produced such a high proportion of hemolysins that lethal injections of the antigen could not appreciably lower the proportion of antibodies in the rabbit blood. These conclusions are important inasmuch as no test for the measurement of the effect of antihistaminic agents on immunological phenomena has as yet been devised. On the other hand, in an experiment with Pasteur Vallery-Radot, Halpern[44] showed that when rabbits were sensitized with horse serum and then twenty to thirty days later given intramuscular Antergan in doses of 40 mg./kg., followed in fifteen to thirty-five minutes by intravenous administration of horse serum in 3 c.c. doses, no anaphylactic reactions could be observed, although another serum injection within eight to thirty-two hours after the first caused hypotension in eight animals, one of whom died. The surviving animals were all thrown into anaphylactic shock when tested five days later, whereas only one such reaction occurred in seven control animals. Antergan is, therefore, considered as having eliminated the period of anaphylactic tachyphylaxis. The authors state that the P-K reaction in man appears only in three to four hours, rather than one hour after an Antergan injection if a histamine antagonist is ingested two to three hours before the injection.

In an attempt to discover the properties of the new drug, a number of experimental studies were done, including among others, the effect of the ingestion of Antergan upon the erythematous area, provoked by intradermal histamine. Warembourg and his colleagues[45] discovered that doses of 0.6 gm. decreased such an area when taken for three days before the injection was given, larger doses causing a notable diminution but no inhibition of such intradermal histamine injections.

In 1945, in the Foreign Letter Section of the J.A.M.A.,[46] Antergan was described as a histamine antagonist, which caused the pruritus due to serum sickness to disappear in half an hour. It was effective, as well, in urticaria, acute eczema, medical dermatoses, and in asthma. It was not uniformly effective in migraine, and had little beneficial effect in arthralgia or shock. The side effects were described as nausea, vertigo, anorexia, "gastric burns." It was said to be tolerated better by children than by adults. The same letter described Neo-Antergan as being three times as potent as Antergan, as well as less toxic. It was stated that well-tolerated doses cause 90 per cent improvement in asthmatic patients. The histamine production was not inhibited but an ability to react to histamine was lost by the tissues during treatment with the drug.

The treatment of bronchial asthma with Antergan by Strengers and his co-workers[47] had as its object the determination of histamine level in the blood of asthmatic patients; the relation, if any, between the histamine level and the severity of the asthma; the therapeutic effect of Antergan and whether the success of Antergan treatment was related to an initially high histamine level in the blood. For this pur-

pose, the authors treated forty-six asthmatic patients, administering Antergan orally and by injection. The histamine levels were determined by Code's method, the normal being taken as between 3 and 13 mg./100 ml. No correlation between the histamine level and the duration of severity of the asthmatic complaints at the time the blood samples were taken was found. Eight cases of twenty-three are reported as giving excellent results; six fairly good and five no improvement. In four patients, the first course of treatment gave good results, but the patients did not respond to a second course given several months later, following a relapse. There was an initial elevation of the histamine level in ten of the twenty-three patients and all of these ten improved. Of twelve patients with normal histamine levels, six improved and six did not respond. The authors concluded that there were two groups of asthmatic patients; those with normal and those with elevated blood histamine levels. They suggested that the low levels in some patients might be due to the intervention of some defense mechanism, although there was no direct evidence for this conclusion, with favorable results seen in some patients as compared to the complete lack of response in others, which suggested the possibility of a "histamine-asthma" group. The response of four patients to the first course and not to the second might demonstrate that the drug lost its effectiveness upon continued administration. The authors felt, however, that Antergan should be given to asthmatic patients who had a high blood histamine level.

Further clinical studies with Antergan by Serafini[48] showed that the drug did not suppress gastric hypersecretion as caused by histamine, although it caused a constant increase in potassium and slight variations, generally decreases, in blood calcium. Serafini reported Antergan as giving beneficial results in eighty-four of 140 cases of allergic disorders, the best results being obtained in acute and chronic urticaria, pruritus and hay fever. Secondary reactions were observed in forty-five patients. In a later study, Serafini[49] reported the effect of Antergan and also of Neo-Antergan, Antistine and Phenergan as well as Benadryl upon histamine and allergic wheals in normal and allergic individuals. Intravenous administration caused antihistaminic effects which occurred much sooner than after oral administration, which was not constant in its time, perhaps because of the different absorption rates of each drug. Skin reactivity, although inhibited, returned to its previous state two days after the drug was discontinued. Undesirable, but not serious, side reactions occurred in 25 per cent of the patients treated. The 140 patients previously described as receiving Antergan could be divided into three groups, of whom eighty-four (60 per cent) were completely relieved; thirty-six (25.6 per cent) were partially relieved; and twenty (14.4 per cent) showed no improvement.

In common with the other antihistaminic agents to be described below, Antergan has been used in non-allergic spasmodic conditions. Ameline[50] used it and Neo-Antergan in the treatment of dysmenorrhea. Beginning when pain first appeared, the patients took Antergan in doses of 0.05 gm. every hour until they obtained relief. They refrained from other medication. The total dose never exceeded 0.5 gm. Some patients required two courses of treatment the remission varying from eight to fourteen months after a single course of antihistaminic therapy.

Antergan has also been used in the treatment of Parkinson's disease by Gerest and Nicollet.[51] Three patients were improved markedly and one temporarily. The treatment failed completely in three patients and was not much more successful in three others. The akinesia was most favorably affected.

The effect of antihistaminic agents on patients with peptic ulcer was studied at an early date. Doscherholmen[52] reported on Antergan (Lergitin in the original paper) in spontaneous and histamine-stimulated gastric secretion as seen in nine patients, five of whom has gastric ulcers, three dyspepsia and one hypertension. A single dose of 0.2 gm. increased, but did not affect the spontaneous secretion in nine. The secretion was stimulated by the subcutaneous injection of 0.1 mg./10 kg. histamine in four of

six tests. Free hydrochloric acid was unchanged or increased in seven of nine tests of spontaneous and in all of six, histamine stimulated secretion patients. The same response occurred with ulcer patients as with others.

Since some of the antihistaminic agents are locally anesthetic, it has been considered that their effect was more anesthetic than antihistaminic. Halpern and his colleagues[53] recently studied the relative local anesthetic power of Antergan, Neo-Antergan, Phenergan and several other RP substances by measuring corneal sensitivity, using cocaine anesthesia as a standard. Antergan was found to be equal in anesthetic power to cocaine, Phenergan was three times as potent, and other RP compounds, much more so. Neo-Antergan, however, had no anesthetizing power. No constant relationship was discovered between the anesthetizing and the antihistaminic properties.

ANTISTINE

Antistine, being one of the earlier antihistaminic agents, has been the basis of a great deal of experimental work, both in and out of the field of allergy. Linde[54] showed that the gastric secretion elicited in anesthetized dogs by the administration of histamine was effectively inhibited by doses of 0.1 gm. of Antistine intravenously, with pre-treatment with Tween 20 administered intravenously at the rate of 1 mg./kg. of body weight per hour. No such inhibition occurred when the administration of Tween did not precede that of Antistine.

Ashford[55] demonstrated that the subcutaneous administration of 100 mg. of Antistine in normal saline, alone, or fifteen minutes before or fifteen to thirty minutes after the subcutaneous administration of 1.5 mg. of histamine acid phosphate in ten healthy subjects did not lower the concentration or output of hydrochloric acid or pepsin, and in some cases, increased them. No reduction in gastric secretion or clinical improvement occurred in two patients with gastric ulcers given 100 mg. of Anthisan orally three times a day for seventeen and twenty days, respectively. One patient became worse. Similar experiments were done with Benadryl (50 mg.), with equivalent results.

With the present interest in desoxycorticosterone, an experiment showing its effect and that of antihistaminic drugs on histamine shock is of special interest. Gross[56] removed the adrenal glands of guinea pigs in two sessions, keeping the animals alive after the removal of the second gland by the subcutaneous injection of 25 mg. of a suspension of desoxycorticosterone crystals, the dose being repeated every five to six weeks. In total, fifty-two animals were operated upon, with a mortality of 20 per cent within the first week after complete adrenalectomy. Histamine, given as a 2 per cent aerosol, caused dyspnea and later, coma. At this stage of the experiment the animals were removed from the bell-jar in which they had been kept and usually recovered. Additional doses of desoxycorticosterone acetate (25 mg./kg.) given one hour before the histamine did not prevent the development of bronchospasm in the adrenalectomized animals, but Antistine, 3 mg./kg., did. In normal animals, desoxycorticosterone, in oily or water solution (10 mg./kg.) did not prevent bronchospasm caused by histamine aerosol.

Staub,[57] one of the first workers in this field, used Antistine in an experiment concerned with epinephrine-histamine regulation. The fact that after the intravenous injection of epinephrine there is a rise in the histamine content of the blood formed the basis of a study of ten patients in whom the antihistaminic effect of Antistine was determined. Antistine in the 200 mg. dose was injected intravenously and then nine minutes later, 0.2 mg. of epinephrine was injected by the same route. The course of the pulse rate and systolic and diastolic blood pressures were then carefully followed, with estimations of blood histamine, using Code's method on the isolated guinea pig ileum. The mode of action of antihistaminic agents had previously been explained

by Halpern as either depending on the inhibition of histamine formation, an acceleration of the destruction of histamine, or the lack of effect of the histamine present on the cells. Staub believes, however, that Antistine acts by inhibiting histamine formation. The antagonistic action of antihistaminic compounds to exogenously produced histamine leads to a displacement of histamine from the receptor cells and the experiments explain the adrenergic effect of these compounds. An antagonistic effect cannot be demonstrated *in vitro,* because the procedure for the estimation of histamine destroys the antihistaminic compound. *In vivo,* however, there is very little histamine production after the administration of Antistine, probably because the drug prevents either the entrance or exit of histamine from cells and cell surfaces.

Of special importance, if corroborated, is the paper by Stavraky,[58] who investigated metallic compounds as possible activators of histaminalytic agents. He discovered that while potassium and calcium were ineffectual, ferrous sulfate increased the effectiveness of small doses of Antistine in counteracting blood pressure changes induced by histamine, injected into decerebrated vagotomized cats. Further experiments on eight patients with seasonal hay fever and asthma due to ragweed pollen showed that the administration of calcium and potassium, given in conjunction with such drugs was ineffectual, although ferrous sulfate by mouth in daily doses of 20 to 45 gr., added to Antistine or to Pyribenzamine was most effective in alleviating the allergic manifestation, relieving as well the lassitude and drowsiness seen in side reactions. When ferrous sulfate was given, the doses of Antistine and Pyribenzamine could be increased. The iron compound was given with calcium, in order to reduce its toxicity, since some patients took 0.5-0.6 gm. of ferrous sulfate four or five times daily. It is interesting to note that one patient, in spite of having taken 600 mg. of Antistine daily, developed bronchial asthma, which was not materially helped by epinephrine in oil. When given the iron therapy in addition, he was relieved from asthma within forty-five minutes and was able to continue in comfort throughout the remainder of the pollen season.

The use of Antistine in ophthalmic conditions suggested a study of its toxicity. Schlaegel[59] instilled 0.5 per cent solution of hydrochloride repeatedly in ten human eyes, producing no discernible corneal damage. Bulbar congestion and subjective stinging were slightly greater with Antistine than with control solutions. Antistine applied to the completely denuded rabbit cornea demonstrated that 0.25 and 0.5 per cent solutions did not delay healing longer than did the control solution. The 1 and 2 per cent solutions, however, were definitely toxic. The 0.5 per cent solution, applied as drops twelve times daily to the eyes of ten human volunteers, failed to affect the size of the pupil or the accommodation. Animal experiments by Yonkmann and his colleagues[60] showed that 3 drops of 0.5 or 1 per cent solution of Antistine instilled into the eyes of rabbits, delayed or abolished the wink reflex for twenty to thirty minutes. Three successsive applications of 3 drops of 0.5 or 1 per cent solution of Antistine or of Pyribenzamine, at three to five-minute intervals into the eyes of six subjects, produced anesthesia of the conjunctiva in ten to fifteen minutes. No pain, hyperemia or pupillary changes occurred.

Hurwitz[61] described the use of Antistine in isotonic solution for the treatment of forty-two to fifty patients with ocular allergy, in which the drug gave moderate to complete relief for the itching, photophobia, lacrimation, conjunctival injection, blurring of vision, secretion and general ocular irritability. The greatest improvement was shown by twenty-three patients with hay fever, with or without other allergic or pathological conditions. Seven of eleven patients with ocular allergy without hay fever improved, the four who failed to improve being sensitive to house dust. Four patients with vernal catarrhal conjunctivitis achieved symptomatic relief and varying degrees of improvement were described as well in nine of twelve patients with palpebral dermatitis, urticaria, eczema, and angioneurotic edema. In some patients, the instillation of the solution was supplemented by application of

Antistine ointment, the use of moist packs of the solution, and oral administration of 300-400 mg. in tablet form. A number of conditions, including hordeola, chalazions, ulcerative blepharitis, and acute conjunctivitis, did not respond until antibiotic or chemotherapy had resolved the superimposed pathological conditions. The side effects were limited to momentary smarting, and in one instance, a hollow sensation of the eye. Grossman and Loring[62] proved the solution useful in nodular episcleritis, having treated twenty-two patients suffering from acute attacks with topical instillation, giving three times daily. Three patients obtained subjective relief in twenty-four hours, eleven in twenty-four to seventy-two hours, and seven in three to seven hours. Only one was not relieved. The redness and nodular elevation of the eye subsided in a few days after symptomatic relief began. Daily and Daily[63] confirmed these studies using the combination of 0.5 per cent Antistine with 0.015 per cent Privine, instilled as drops into the conjunctival sac of 100 patients for a number of ocular conditions, including blepharospasm, kerato-conjunctivitis sicca, scleritis, episcleritis, and irritation following trauma. The patients showed a rapid decongestion of the conjunctiva with alleviation of the subjective and objective symptoms.

Antistine has been found useful in the treatment of migraine, Biro[64] finding it to be as effective as ergotamine in arresting migraine attacks. His report states that the drug can be given orally, subcutaneously, intramuscularly, and intravenously during the periods when the patient is symptom-free. Of eleven patients so treated, nine remained free from attacks and in two others the attacks became less frequent, with no toxic reactions being noted.

Of interest is the report by Timonen and Zilliacus[65] on the use of the Antistine on twelve patients with allergic dermatoses and sludged blood as shown by small red blood cell aggregations in the conjunctival vessels. Of these patients, seven were given 50 mg. heparin intramuscularly four times daily, or initial intravenous doses of 100-150 mg. followed by 50 mg. intravenously four times daily to a total of 50-1500 mg. Three patients were given 0.1 gm. Antistine intramuscularly or intravenously, followed by 0.005-0.1 gm. orally three times daily, one patient receiving oral doses only. Heparin relieved both the aggregations and, except in one case, the dermatitis, but cutaneous relapses occurred in three instances. The Antistine produced a decrease in the rate of aggregation during treatment to a lesser degree than Heparin, and in most cases, the dermatosis decreased or disappeared. In one thirteen-year-old patient with a dermatosis of two years standing and relatively abundant aggregation, the initial intramuscular dose of Antistine produced a clear diminution of the aggregation within fifteen minutes and in six days, during which time 0.05 gm. was given three times daily orally, the skin condition practically clearing. The sedimentation rate was not affected. In one patient, who was not improved with Antistine, there was swelling of the wrists and face, with a decrease in urinary output. These symptoms subsided when the drug had been withdrawn.

Brack[66] used Antistine for a period of eighteen months in more than 100 patients suffering from urticaria, eczema, neurodermatitis, prurigo, lichen rubber planus, psoriasis, and nervous pruritus, without skin changes, as well as in scabies. He stated that it was occasionally necessary to use doses which caused temporary mild dizziness, in order to have complete suppression of the pruritus. In urticaria, not only was the itching suppressed, but the skin changes were counteracted or prevented. Direct influence upon the skin could not be proven, however, in eczema and neurodermatitis, prurigo and other skin defects, but the indirect therapeutic effect was considerable because the suppression of the pruritus facilitated the effectiveness of other treatment. A parallel study with Antergan showed it to have numerous undesirable secondary effects. The Antistine seemed to suppress the pruritus, regardless of whether the itching was due to sympathicotonic or parasympathicotonic factors, indicating to the authors that pruritus was not always produced by H substances.

Kallós[67] used Antistine for the same condition, and in addition, for serum sickness and drug exenthemata, as well as for migraine and Ménière's disease. He found that it had little effect in bronchial asthma or migraine. The toxicity was slight and the drug could be used orally, intramuscularly, intravenously, or applied directly to the mucous membranes of the eye and nose. Good results were achieved in vasomotor rhinitis, angioneurotic edema and urticaria, with poor results in asthma. The side effects were seen in thirteen patients but persisted in only seven on the maintenance dose necessary. Because the majority of the patients with urticaria were women, and in several cases the symptoms were aggravated in connection with the menses, it was suggested that in them there might be an endocrine relationship.

Antistine has been found useful in contact dermatitis. Cunz[68] described "anaphylactic shock" following patch tests with various materials including ammonium oxalate, nicotine and suspension of tobacco dust on a patient with contact dermatitis. An intragluteal injection of Antistine in the 0.1 gm. dose caused a rise in blood pressure, normal respiration and the cessation of vomiting within fifteen minutes. Hughes[69] reported good clinical results in nineteen of thirty-two patients with bronchial asthma, allergic coryza, eczema, contact dermatitis, urticaria, pruritus or blepharitis. The patients received 100 mg. of Antistine every three to four hours, some of the patients being treated with the same drug subcutaneously. Eighteen per cent of the patients reacted with headache, dizziness, or nausea, but the reactions were seldom sufficiently severe to warrant discontinuance of treatment. Hughes feels that the drug is more useful in acute than in chronic conditions. Britton[70] used Antistine similarly in fifty-four patients, of whom thirty-eight were improved, twenty-four markedly, and fourteen moderately. The patients were given two 0.1 gm. tablets daily, one on arising and retiring, and if there were no side reactions, the dose was gradually increased to a maximum of two tablets, four times daily. His patients suffered from the following conditions: hay fever, urticaria, vasomotor coryza, pruritus ani, allergic conjunctivitis and migraine. All of the patients relapsed when the drug was withdrawn. Toxic reactions—nausea, drowsiness and headache—occurred in twenty patients, being sufficiently severe to warrant cessation of treatment in seven. Antistine was found effective in some patients who suffered severe side reactions with other antihistaminic drugs and vice versa. Britton feels that the first dose, or any increase, should be given at a time when the patient will not be called upon to perform skilled movements, depending upon acts of judgment, as, for instance, driving an automobile.

The return of symptoms upon cessation of therapy is sometimes accompanied by the additional syndrome of withdrawal symptoms, as described by Cherry,[71] whose report is concerned with labyrinthitis as experienced in three patients, who suddenly ceased antihistaminic therapy, after taking the drugs for prolonged periods of time. One patient took Antistine, another Anthisan, and a third, Benadryl. Administration of one tablet of the responsible drug relieved the symptoms within two hours, but desensitization with decreasing doses of the responsible drug required two and six weeks in the first and second patients and a very short period of time in the third.

The indications for the administration of Antistine, based on the experience of treating eighty-seven patients, are listed by Overton[72] as the presence of urticaria, angioneurotic edema, eczematous conditions with edema, and itching. He administered increasing doses of the drug until the therapeutic effect, or toxic manifestation occurred, or until 800 mg. was being taken daily, as given locally, orally or intramuscularly. He reports beneficial results in twelve of thirteen patients with chronic constitutional eczema, one with varicose edema, three more with constitutional eczema, four with sensitization dermatitis, one with dermatitis herpetiformis, one with lichen obtusus corneous, two of four with lichen planus, one with mycosis fungoides, two of four with senile pruritus and thirteen of sixteen with chronic urticaria. The drug was without effect in two patients with actinic dermatitis, three with cheiropompholyx, eight with infantile eczema, two with erythema muliforme, two with pem-

phigus vulgaris, one with psoriasis, fourteen with pruritus ani or vulvae, and six with urticaria papulosa. The side reactions included dizziness and light-headedness in ten, vomiting in one, convulsions in one, collapse in one, disorientation in one, and local induration and soreness after injection in three patients. The doses for children were not over 200 mg. daily. The author concludes that although both drugs are therapeutically equivalent, Antistine causes fewer side reactions than Benadryl.

Hudson[73] chose for his clinical trial with Antistine, those patients who were unaffected by Benadryl or Pyribenzamine or who had to discontinue treatment because of the side effects. Of twenty-one patients given Antistine, only one patient suffered from double vision and this was relieved by reducing the dose to below 200 mg. four times daily. The best results were obtained in eight patients with urticarial disorders, all of whom were markedly improved. Of four patients with atopic dermatitis, however, only one completely cleared, but there was a reduction in pruritus of the other lesions. No patients with the pruritus ani or erythromelalgia were relieved and in only two patients with senile pruritus was there moderate improvement. In two cases, the drug was given intravenously with excellent results.

Studies in this country by Kaplan and Ehrlich,[74] on ninety-five patients given 100 mg. of Antistine three or four times daily for seven to 133 days, showed thirty of thirty-nine patients with hay fever, eight of nineteen with allergic rhinitis, and sixteen of twenty-two patients with bronchial asthma reporting excellent or good results. Three of four patients with chronic urticaria and two of four with atopic eczema and one of two with contact dermatitis reported poor results. The untoward reactions, including nausea, sneezing, dryness of the mouth and dizziness in thirteen patients necessitating discontinuation of the drug in only one.

The pruritus treated need not be of typical allergic origin as shown by the report of Gross[75] who administered Antistine for four to five days in sixteen children with varicella, superimposed upon tuberculosis. The drug suppressed the pruritus and caused a general improvement, weight gain and prevention of secondary infection. The course of the disease was shortened, the average duration of fever being 2.8 days in treated children as compared to 5.5 days in the untreated controls. The average duration of the exanthemata was 2.8 days for the treated patients as compared to 6.4 days for the control patients. The fever curve was steeper and shorter in treated patients, the peak, however, being above that of the controls. There was no detectible exacerbation of the tuberculosis.

Levin and his colleagues[76] compared Antistine with Neo-Antergan in the treatment of ragweed hay fever. One hundred and thirty-four patients were divided into three groups; the patients in the first receiving no pre-seasonal or co-seasonal desensitization. Twenty-seven of these were given Neo-Antergan and reported 70 per cent relief, while twenty-three were given Antistine and reported 65 per cent relief. In the second group, ragweed desensitization was given, and in addition, Neo-Antergan in fourteen, giving 79 per cent relief, while Antistine was administered to twenty, effecting 75 per cent relief. Of the third group of patients who received ragweed desensitization alone, of fifty patients, 76 per cent were relieved. Of the total of forty-one patients treated with Neo-Antergan, 36 per cent had one or more toxic reactions, whereas of the forty-three treated with Antistine only 21 per cent reported side effects.

Dickstein[77] substituted Antistine for Benadryl or Pyribenzamine during the height of the ragweed season, giving doses of 100-200 mg. to eight adults and nine children, in whom hay fever symptoms were present at a pollen count of 500 or more. All of the patients were under ragweed desensitization therapy, 88 per cent reporting satisfactory relief with 25 mg. of Pyribenzamine and 64 per cent with Benadryl. The side effects were listed as listlessness and nausea in 60 per cent of the patients, being severe in 18 per cent of the patients given Pyribenzamine. Grogginess and sleepiness occurred in 47 per cent of the patients and was severe in 29 per cent of those given

Benadryl. Antistine gave satisfactory relief in 29 per cent of the patients. Side effects of nausea, listlessness and vomiting occurred in 18 per cent, being objectionable in only 6 per cent. It was noted that of three patients who obtained relief with Antistine, two were children, aged three and three and one-half, respectively, and another was a patient with a very high sensitivity to all drugs. Although the children received relatively high doses, none had unpleasant side effects.

Walton[78] compared Antistine with Neo-Antergan and Pyribenzamine, finding 50 mg. of Pyribenzamine equal to 100 mg. of Antistine. Toxic reactions occurred in 25 per cent of the patients receiving Antistine and in 27 per cent of those given Pyribenzamine. Marked relief of perennial hay fever occurred in four of five patients given 100 mg. of Neo-Antergan. The drug caused a severe exacerbation in one asthmatic patient, but no other toxic reaction. It was successful in two patients who did not respond to the other drugs. Antistine is credited as causing improvement in fifty-one of eighty-three patients, while Pyribenzamine improved twenty-one of twenty-six patients. The conditions treated included seasonal or perennial allergic coryza, asthma, urticaria, atopic dermatitis or migraine.

Using Antistine alone, Friedlaender and Friedlaender[79] reported benefit in nine of twenty-four patients with bronchial asthma, thirty-five of fifty with vasomotor coryza, seven of ten with acute urticaria, three of nine with chronic urticaria, one of six with allergic headache, three of five with atopic dermatitis and three of six with contact dermatitis. The drug neither benefited patients with penicillin urticaria, pruritus ani, nor with unclassified dermatitis. The average dose was 50 to 100 mg. four times daily. A clinical comparison showed that, in general, 100 mg. of Antistine was as effective as 50 mg. of Pyribenzamine. Of eleven patients with allergic conjunctivitis treated with instillation of the 0.5 per cent solution, eight experienecd symptomatic relief.

Comparative studies involving Antistine and other drugs have been written by Arbesman,[80] Waldbott and Young[81] and Gay and his colleagues.[82] Arbesman studied 291 patients suffering from allergic coryza or bronchial asthma, or both. The patients were carefully interviewed at definite intervals, recording their symptoms each day on special cards. A patient was regarded as improved when he had at least 50 per cent relief of his symptoms. Patients were given Antistine, Neo-Antergan and Neohetramine, in 100 mg. doses, Pyribenzamine in 50 mg. doses and Hydryllin (Benadryl, 25 mg.; aminophylline, 100 mg.) in doses of one or two tablets. The patients took the drugs only when required, the daily dose not being stated. Eighty per cent of the patients with allergic rhinitis treated by Pyribenzamine reported their conditions improved and 63 per cent of those taking Neo-Antergan. The other drugs had lesser effects. In bronchial asthma, Hydryllin was effective in 64 per cent of forty-eight patients, with Neo-Antergan effective in 43 per cent and Pyribenzamine in 45 per cent. The lesser potent substances, Neohetramine and Antistine, caused fewer side reactions, although they proved markedly effective in certain patients. Waldbott and Young's patients were given Antistine, Benadryl, Neo-Antergan, Neohetramine, Phenergan and Trimeton. In all, 395 patients were treated, as suffering from hay fever and allergic coryza, urticaria and angioneurotic edema, as well as bronchial asthma. The author reports that the six drugs acted similarly in the degree of relief afforded. The variation and duration of the effect was related to the severity of the condition rather than to the drug used, excepting in Phenergan, which decidedly had a more protracted action, although dizziness and drowsiness were more pronounced with this drug than with any of the others, excepting Benadryl. Since the therapeutic effect outlasted the soporific action by several hours it was used with greatest advantage at bedtime.

The study by Gay includes 686 patients treated with Antistine, Chlorothen, Histadyl, Hydryllin, Neo-Antergan, Pyribenzamine, a drug termed Compound 1913 (described as Compound 1721 in addition to aminophylline). Of 428 patients with

seasonal perennial allergic rhinitis, the drugs benefited an average of 68 per cent, Pyribenzamine helping 75 per cent of 51, Hydryllin 73 per cent of ninety-seven, Antistine 70 per cent of forty-three, and Neo-Antergan 70 per cent of 102. Although nasal obstruction was seldom influenced, the itching of the eyes and nose, the watery discharge and sneezing were relieved. In fifty-three cases of urticaria, Antistine relieved seventeen of nineteen, Hydryllin eight of ten, and Neo-Antergan six of ten, the average being 77 per cent. In fifty-six cases of dermatitis and pruritic conditions of varying origin, Antistine helped twenty-one of twenty-nine patients, and Histadyl nineteen of twenty-seven patients. Severe bronchial asthma required epinephrine and aminophylline and only 40 per cent of ninety-six mild cases responded at all to histaminalytic agents. Gay notes, as have others, that ragweed-hay fever patients, who responded well in the previous season, contracted severe asthma in unusual numbers at the end of the season and could not be helped at all. The side reactions totalled 13 per cent of 110 patients given Antistine and 42 per cent of twenty-six patients given Compound 1913. Histadyl had the second lowest frequency of side reactions (19 per cent). One hundred and nineteen patients complained of drowsiness, the other side effects noted being dizziness, weakness, fatigue, headache, nervousness, tremor, apprehension, tachycardia and anorexia, nausea, abdominal pain, diarrhea, dryness of the mouth, blurred vision, dysuria and urinary frequency. Severe side reactions occurred with 18 per cent of 142 patients given Hydryllin, and 25 per cent of seventy-one patients who took Pyribenzamine. The critical dosage of Antistine was discovered to be 400 mg. daily, while that of Hydryllin was 100 mg. and that of Histadyl, 200 mg.

Late in 1945, McElin and Horton[83] published the earliest report on the use of Benadryl in eighty-one patients, describing it as giving excellent results in thirty-seven patients, with good results in eleven others suffering from allergic conditions not amenable to any other form of treatment. Twenty-one of twenty-two with seasonal hay fever achieved 50 per cent relief and nineteen obtained 75 per cent or greater relief. Three patients with Ménière's disease were completely relieved within twenty-four hours. Three patients allergic to penicillin, and a fourth, allergic to the barbiturates, obtained relief from pruritus in two to four minutes, with the lesions disappearing in eight in twenty-four hours. Patients with recurrent contact dermatitis, trigeminal neuralgia, physical allergy, characterized by irritation of the eyelids and photophobia showed only slight improvement. Intravenous injections were given to patients with dysmenorrhea, hay fever, vasomotor rhinitis, and histaminic cephalalgia, all being relieved rapidly in some, in thirty seconds. In an epileptic patient intravenous administration of 60 mg. aborted an attack. Sleepiness, dizziness, dry mouth and nervousness occurred in ten of the seventy-four patients who received Benadryl orally. Other side effects noted were frequency, fatigue, epigastric distress, inco-ordination, nausea, bad taste, bleeding tendency, sense of relaxation, diarrhea, constipation, excessive perspiration, tinnitus and blurring of vision. One patient developed a generalized pruritus.

In Logan's series[84] there were eighteen children, the dose being 2 mg./lb./day given in two to four doses. If there was no result in thirty to forty minutes, the dose was considered inadequate. In a two-year-old child, a 10 mg. dose effected disappearance of hives within thirty minutes, with relief being maintained while treatment was continued. Benadryl was also used before plasma infusions, obviating reactions, as well as in the treatment of the generalized urticaria and swelling due to tetanus and gas gangrene antitoxins. The only toxic symptoms seen were drowsiness and vomiting, and local anesthesia of the tongue.

Feinberg and Friedlaender[85] administered 50 mg. of Benadryl five hours, three hours and one hour before skin-testing thirty dermographic patients, with temporary partial or complete control of whealing. The drug, however, did not prevent specific skin reactions to all allergens, including pollens, fungi, house dust, danders and some

foods. No improvement was noted in twelve patients with allergic rhinitis, seventeen with asthma or two with chronic urticaria, while two other patients with chronic urticaria obtained almost complete relief.

Studies on sixty normal and 242 allergic individuals were initiated by McGavack et al.[86] It was discovered that Benadryl suppressed the dermal response to histamine in both types of patients, depressing the gastric acidity in twenty of twenty-one subjects, decreasing capillary permeability and lowering the systolic blood pressure of twenty-nine of seventy-four patients by 10 mm. or more when 250 to 600 mg. of Benadryl were given for twenty-one to 280 days. Glucose tolerance was increased following 20 mg. given intravenously. Benadryl also exerted an atropine-like activity on the eyes of forty-three of sixty subjects when the 0.5 per cent aqueous solution was applied. Fewer than half of the patients with eczema and neurodermatitis were benefited, but 60 per cent of the patients with bronchial asthma, hay fever, vasomotor rhinitis, allergic hydroarthrosis, functional dysmenorrhea, spastic colon, migraine and Ménière's syndrome were helped. The drug was less effective when used for treating intractable insomnia, cardiac asthma, hypertension or epilepsy. Of the 242 patients, 131 reported untoward reactions, especially drowsiness. The highest percentage occurred in the patients who required 150 mg./day. Drowsiness, however, was occasionally seen with doses as small as 50 mg. In five cases, withdrawal of the drug was necessary. Although clinical response usually followed in twenty minutes, it was sometimes delayed twelve to thirty hours.

Bain and his co-workers[87] measured the effect of Benadryl upon intradermal histamine reactions in eleven men following a single oral dose of 100 mg. Anthisan, in the 200 mg. dose, and Phenergan in the 50 mg. dose, were used for comparison. Benadryl barely reduced the wheal response after three hours, while Anthisan and Phenergan caused significant reductions of the flare and wheals within one hour, the effect lasting twenty-seven and thirty-two hours, respectively. The patients who showed poor specific response to one drug, also showed poor specific response to the others, but responded normally when the doses were increased. Twenty patients with chronic urticaria given Anthisan indicated that the dosage necessary to suppress or modify the wheal was the same as that known to cause modification of urticaria. All three drugs caused side reactions, which were greater with higher doses. Perry and Hearin[88] used histamine iontophoresis to determine the duration of antihistaminic activity of orally-administered compounds. Their normal subjects included nineteen males and twenty-six females, varying in age from nineteen to forty-three years. The maximum antihistaminic activity of Benadryl, but also of Pyribenzamine and Hydryllin, was reached in two hours after the ingestion of each of the three drugs in thirty-seven patients; and three hours in the remaining eight, probably because of slow absorption. The effect had completely disappeared in five hours in all but two subjects, and almost so in these.

Since histamine stimulates the secretion of hydrochloric acid, it was logical to theorize that an antihistaminic agent would inhibit the process and would, therefore, be useful for the treatment of peptic ulcer. In animals, such an effect has not been consistently seen. There are some reports in the literature and oral antihistaminic therapy has relieved peptic ulcer symptoms. These, of course, may be due to the anesthetic effect of the drug, or may be coincidental results. In any case, Gilg[89] reported that 50-100 mg. Amidryl (Benadryl) resulted in an increased reaction to subcutaneous injection with 0.5 mg. histamine in nine patients, increasing the volume, the free acid and the total acidity of the gastric secretion. Administration of the solution of Amidryl directly into the stomach in the absence of histamine resulted in increased gastric secretion, or increased acidity in four individuals. Gilg believes that Amidryl acted as a synergist with histamine in the original experiment. Alsted[90] gave Amidryl (Benadryl) to twenty patients with gastric or duodenal ulcer. Thirteen received 400 mg. of Amidryl daily for four weeks and seven received antacid

therapy. Following the administration of 0.5 mg. of histamine, gastric secretion was suppressed in six of the Amidryl patients and remained unchanged in four. Results in three patients were inconclusive. No such depression of gastric acidity was observed in seven patients treated with antacids.

McGavack, et al[91] determined the levels for Benadryl in blood and urine following a single oral administered dose. The blood values began to rise within sixty minutes and reached an average peak of 1.07 micrograms/c.c. between ninety and 120 minutes. Pyribenzamine used as a comparison showed an appreciable rise, first evident at 120 minutes, with the trend still upwards at 180 minutes. Within the first twenty-four hours, 46.0 and 20.1 per cent of the ingested Benadryl and Pyribenzamine, respectively, were excreted in the urine.

In 1947, there were a number of reports of patients who developed hypertension during the administration of Benadryl. Gelfand[92] described a hay fever subject whose pressure rose from 138/85 to 200/110 following its ingestion. A colleague informed the author that he had had two similar cases. Mackmull[93] injected fifty patients with intravenous Benadryl in doses of 50, 75, 100, 200 and 300 mg. The average systolic and diastolic blood pressures were elevated after all, particularly with the doses of over 100 mg., although none of the patients were hypertensive. The use of large intravenous doses of Benadryl is contra-indicated in the presence of hypertension. Electrocardiographic changes of sufficient significance occurred after the 200 and 300 mg. doses to preclude the use of such treatment in patients with heart disease.

Reinstein and McGavack[94] performed standard glucose tolerance tests on 17 subjects who were maintained on a basic diet for 3 days before the first test and throughout the entire period of study, excepting on the days when the tests were taken, three tests being performed on each subject. Benadryl intravenously was shown to cause a significant increase in sugar tolerance in all patients, irrespective of age. In order to rule out any normal variation in glucose tolerance when determined at three-day intervals, three subjects were given the same regime as the fourteen test subjects mentioned, excepting that no medication was used in conjunction with any of the three tests on those subjects. These same authors[95] have recommended that Benadryl be used in doses of 50 mg., three times daily, increased by 50 mg. every day until symptomatic relief is obtained, stating that up to 600 mg. daily can be given safely by this method. The minimum effective doses continue for two weeks. They state that side reactions can often be eliminated by starting with smaller doses and giving the drug during or immediately after meals, with tolerance usually establishing itself with twenty-four to ninety-six hours. Of 313 patients suffering from various allergic conditions and related diseases, 141 obtained complete relief and seventy-eight were improved after Benadryl treatment which lasted for two weeks in acute cases; for one year in chronic conditions. Zolov[96] treated his patients with a 10 to 25 mg./c.c. dose given intravenously during two minutes, on one or more occasion, one of his twenty-six patients receiving a 30 mg. in 100 c.c. of saline over a ten-minute period. Good to excellent results were seen in all but six of fourteen patients with bronchial asthma, and all but one of four with ragweed hay fever, three with vasomotor rhinitis, two with neurodermatitis, and one each with poison ivy, angioneurotic edema and dermatitis medicamentosa. In three of the patients with acute bronchial asthma and hay fever, relief occurred in five to fifteen minutes, the patients remaining free of symptoms for three to four hours. The poison ivy pruritus was relieved for six hours. The reactions included nausea in one patient following a 15 mg. injection, intense headache beginning in one hour after a 20 mg. injection, the symptoms lasting twelve hours. A third patient suffered chills beginning one hour after the injection and lasting for thirty minutes.

In 1946, Slater and Francis[97] described Benadryl as a contributing cause of an accident. The patient, who drove an electric cargo platform truck, lost control of

the machine and jumped clear, following which it went off the platform and was wrecked. Reports of unusual side reactions began to appear in rapid succession. Borman's case[98] suffered from mental lethargy, mental confusion and disorientation. Weil's case[99] responded with muscular epileptiform twitching, slurring of speech, inco-ordination and nervousness as manifested by singing and laughing during normal sleeping hours, following 100 mg. doses, the 50 mg. dose causing no symptoms. The patient described by Geiger et al[100] responded to Benadryl with pallor, low blood pressure and a general shock-like reaction with diminished vision, drowsiness and pyrosis. The length of time reactions can occur was demonstrated by a patient of Schwartzenberg and Willerson,[101] who responded to Benadryl with neuritic and gastrointestinal symptoms, pallor, drowsiness, general malaise, an inability to co-ordinate thought and speech, and numbness and tingling in the extremities. The patient had taken twenty-three capsules of 50 mg. each in twenty days, the reactions lasting approximately three months. Duerfeldt's patient,[102] a three-year-old child, took 700 to 800 mg. of Benadryl accidentally. Symptoms of nervousness and muscular twitching occurred within fifteen minutes, followed by convulsions and respiratory collapse. Among other things, the patient was given Dilaudid (2 mg.) and histamine, 3 mg. Asthmatic rhonchi were noted in forty-five minutes after the histamine was administered and repeated doses of epinephrine (0.1 c.c.) were required to control the asthmatic breathing. The convulsions were finally controlled with 30 c.c. of 50 per cent ether in oil administered rectally, the ataxia gradually decreasing by the fourth post-treatment day. Duerfeldt also mentions a teen-aged girl, who took thirty of the 50 mg. capsules with a successful suicidal intent. Sands[103] describes acute gastric and renal irritation lasting forty-eight hours in a patient following the oral administration of six Benadryl capsules in three days, and Swartz[104] reports tinnitus, vertigo and nystagmus in a thirty-two-year-old patient who took 550 mg. of Benadryl in six days. His symptoms subsided on the seventh day of treatment with ephedrine and ammonium chloride. They were reproduced on two subsequent occasions by administration of small amounts of Benadryl in elixir and powder form. Convulsions, protrusion of the tongue, bulging eyes, cyanosis and threshing movements of the arms and legs developed in a normal child one-half hour after the accidental ingestion of approximately 50 mg. of Benadryl. Starr and Rankin[105] reported that the patient gradually improved during the next twenty-four hours after gastric lavage and the administration of magnesium sulfate, phenobarbital, and sodium Amytal. The length of time such symptoms may persist is shown by the report of Pereira,[106] whose patient took 300 mg. of Benadryl in three days, developing nausea, vomiting, diarrhea, somnolence, hallucinations, temporary blindness and internal strabismus. The symptoms abated within four days, excepting for those referred to the eye, which disappeared in one and one-half months, with residual hemianopsia in one eye. Impotence, a symptom which may have escaped early observation, was described by Jennes.[107] It followed the use of Benadryl, Pyribenzamine and Thephorin in one patient, although Benadryl caused no such effect in the second patient. A complete review of the toxicity of Benadryl has been assembled by Sachs.[108] A reprint or photostat copy should be in the hands of every allergist who prescribes antihistaminic agents. The following list, repeated for emphasis, includes all the effects culled from the literature by Sachs and mentions a number of others since reported upon. It should be noted that these reactions are of the more obviously superficial functional type. Long range studies have not been done for possible deep-lying changes which only time and investigative perspicacity may uncover. The reactions so far known vary from slight drowsiness, at the best, to fatal toxicity, at the worst. The greater number of reactions are neuro-psychiatric and all of the following have been described: drowsiness, dizziness, faintness and fainting attacks, mental confusion, difficulty in co-ordination, disorientation, narcolepsy, stupor, coma, giddiness, general hallucinations, apprehension, nervousness, weakness, fatigue, head-

ache, amnesia, lassitude, choking and slurred speech, somnambulism, exhaustion, irritability, athetoid movements, spastic jactations, acute melancholia, suicidal tendencies, peripheral neuritis, bilateral tinnitus, insomnia, tremor, sense of relaxation, mental lethargy, "walking on air," acute hysteria, jerky and rapid speech, and "an all gone feeling at the pit of the stomach," as well as a generalized numbness. In the ocular system, patients have complained of photophobia, dimming of vision, dilated pupils, difficulty in accommodation and blurring of vision, as well as visual hallucinations, and rapid nystagmus. There may be complaints of muscular aching and twitching, low back pain, genito-urinary symptoms such as impotence, incontinence, frequency and bladder discomfort. In the respiratory and alimentary tracts, the patient may complain of a dry nose, dry oral cavity, olfactory hallucinations, bad taste, "chloroform-like taste," nausea, vomiting, epigastric distress, indigestion, pyrosis, sore tongue, abdominal cramps, diarrhea or constipation. In some patients, ingestion has caused bronchial asthma and also respiratory arrest requiring artificial respiration. In the cardiovascular system, the response has been vasospasm of the fingers with pallor, hot flashes, shock-like reaction and chills, as well as excessive perspiration, or cold extremities, orthostatic hypotension, true hypotension, facial edema, elevated pulse rate, palpitations and a tendency to bleeding. Aggravation of the original symptoms has been seen, as well as generalized pruritus and urticaria. Skin manifestations following the ingestion of antihistaminic agents include eczematoid dermatitis, pityriasis-rosacea-like reactions and erythemato-papular eruptions.

Comparative studies of the toxic manifestations of Benadryl and Pyribenzamine have been done by McGavack et al,[109] some reactions occurring in forty of the fifty-two patients who received only Benadryl, and thirty-five of fifty-two receiving Pyribenzamine. The most common symptoms noted were drowsiness, oral dryness, dizziness, weakness and nausea. A tendency to establish tolerance was more evident with the former rather than the latter drug, but at dosage levels of 300 mg./daily, the incidence of reactions was approximately equal. At levels of 450 mg./daily, Benadryl was definitely more toxic. Holtkamp et al[110] compared the side effects of Benadryl, Pyribenzamine and Hydryllin in normal college students, the medication being given three times daily with food. It was discovered that by the Bourdon test that there was an appreciably altered mental ability as demonstrated also by the reaction time using an impulse counter and the minimum distance two-point discrimination test. Benadryl heightened the response in twelve subjects, Pyribenzamine in six and Hydryllin in sixteen. Benadryl and Hydryllin also decreased the response in eleven subjects and Pyribenzamine in fifteen. The decreases caused by Benadryl were of greater magnitude than those caused by Pyribenzamine. In two patients the slow motor response was sufficient to incapacitate them, while drowsiness, headache and dizziness occurred after 50 mg. of Benadryl in one patient. Benadryl and Hydryllin tended to lower the systolic and diastolic blood pressures of six subjects and reduce the respiratory rate in seven.

Of the fatalities known, only two have been chosen for description. The patient reported by Blackman and Hayes[111] died following the second of two oral doses of 100 mg. Benadryl, the acute bronchial asthma being exacerbated, Benadryl causing severe depression of the central nervous system. The same patient had received 50 mg. of Demerol and 1½ gr. of phenobarbital, given with other supportive measures following the appearance of the alarming reaction. The patient described by Davis and Hunt[112] had taken a dose of 474 mg. by accident.

All of the reactions so far described are those of oral administration. McGavack et al[113] tested the effects of topical applications, using four different ointment bases and strengths of 2 to 5 per cent in sixty-three subjects. The concentrations listed completely destroy the response of the skin to intradermally applied histamine. Polyethylene glycol monostearate and oil and water emulsions appeared to be the best bases employed. In seventy-four patients with itching dermatitis, forty-four obtained com-

plete relief and, in addition, eighteen were improved. Six patients experienced discomfort from the application of the ointment, particularly with a 5 per cent concentration. In two patients this was shown as due to the base, and in another, to the aggravation of the weeping eczematous lesions. There were no systemic side reactions.

The use of antihistaminic agents, especially Benadryl, in the treatment of reactions to penicillin has been published in detail in the author's review on reactions to penicillin.[114] In brief, the recommendation of Pillsbury et al are followed. The penicillin therapy is discontinued as soon as symptoms occur, and Benadryl or Pyribenzamine given orally three to six times a day in doses of 50 to 100 mg. or 5 to 10 mg. intravenously in 20 c.c. of isotonic saline. The antihistamine drug administration should be continued with amounts decreasing gradually if the response to a new brand of penicillin is good, or increased if urticaria persists or recurs. According to Taplin and Bryan,[115] a 1 per cent Benadryl solution can be used with micronized penicillin for the aerosol treatment of patients with intrinsic bronchial asthma, Benadryl causing a reduction in cough and a decrease in sputum in 320 such patients. The micronized Benadryl alone, or mixed with vasoconstrictors, is symptomatically effective in asthma after inhalation of 1/10 to 1/20 the usual oral dose. Only eighteen of the 320 patients treated with penicillin potassium aerosol demonstrated allergic reactions.

The use of Benadryl in streptomycin sensitivity has been described by Holt and Snell,[116] whose patient responded with angioneurotic edema and moderate swelling of the lips and face after nine days of treatment. Benadryl in the 50 mg. dose four times daily relieved the condition in twenty-four hours. Bignall and Crofton[117] reported that the nausea and vomiting which sometimes followed the use of large doses of streptomycin could be relieved by Benadryl in 50 mg. doses eight hourly, the morning vomiting recurring when the Benadryl was discontinued, ceasing abruptly when Benadryl treatment was initiated. The substitution of lactose capsules was without benefit. Because of the suspicion that the Benadryl might be acting as a sedative, phenobarbital was substituted with no relief. The patient also was relieved by Antistine.

Contact dermatitis due to streptomycin, however, is not affected by Benadryl as described by Cucchiani and Erdstein,[118] who treated seven nurses who had been exposed to streptomycin, responding with pruriginous papules and vesicules, fissures, desquamation, exenthemata of the fingers, elbows and eyelids. Antistine was also ineffective.

Benadryl has been used in urticaria due to both liver and insulin. The first, by Nicholson,[119] whose patient responded with urticaria following 2 ml. liver extract injected monthly, with 0.3 to 0.5 ml. of epinephrine. The simultaneous administration of 100 mg. of Benadryl permitted the patient to take treatment safely. Leavitt and Gastineau[120] gave Benadryl orally with complete relief of local and generalized urticaria to an insulin-sensitive patient, the local reaction being prevented by the solution of Benadryl mixed with the insulin. Passive transfer tests revealed the presence of reagins in the patient's serum and direct skin tests gave evidence of the inhibition of Benadryl. With the small dose used (0.5 to 1.0 c.c. of 1:1000 Benadryl) side reactions may be avoided, although in some cases, oral as well as parenteral administration of Benadryl may be necessary to control severe localized or generalized reactions. Exact techniques for the use of antihistaminic drugs in treating patients allergic to liver extract can be found in the reports by Carryer and Koelsche,[121] and for insulin, by Klein.[122]

No review of the antihistaminic drugs would be complete unless mention were made of the numerous non-allergic conditions, which respond to their administration. Among others, convulsive seizures have been treated by Churchill and Gammon,[123] who report that a single intravenous injection of 30 to 125 mg. of Benadryl in ten

patients with true or variant petit mal reduced the spike-wave abnormality as seen in the electroencephalogram, increasing it in two patients with focal discharge, producing motor convulsions in one. The intravenous administration of 8 to 75 mg. of Pyribenzamine to seven patients with petit mal resulted in increased abnormalities in five, but no change in two. Oral doses of 75 to 400 mg. of Benadryl to twelve patients with true petit mal decreased the frequency of attacks in eight, markedly so in four. Oral doses of Pyribenzamine failed to improve the condition of an unspecified number of patients tested, decreasing the generalized seizures in one. The authors urge that antihistaminic drugs should be used with care in treating patients who suffer from convulsive disorders since the drug has been proven to cause attacks. Horton and Brennan[124] discovered that patients with trigeminal neuralgia were benefited by Benadryl in the 100 mg. or Pyribenzamine in the 50 mg. dose. Since atropine and phenobarbital have been ineffective, the authors conclude that Benadryl and Pyribenzamine exerted their therapeutic effects by antihistaminic activity rather than by antispasmodic or sedative reasons. Young[125] treated a patient with herpes zoster, with 50 mg. of Benadryl every four hours, complete cure occurring in five days. The patient also received 10 units of Pituitrin. MacPherson[126] used Benadryl in dysmenorrhea, the dose being one capsule, three times daily beginning the day before the expected period. One of his patients was relieved in ten minutes by 1 c.c. of epinephrine 1:1000, the epinephrine being just as effective on the second occasion. Finch[127] gave twenty-nine pregnant women Benadryl to control their nausea and vomiting. Two of three cases of pernicious, and all of eight cases with severe, vomiting, eleven of twelve with moderate vomiting, as well as all of six with mild nausea and vomiting were completely relieved. Severe cases were given intravenous injections of 50 mg. three or four times daily during the first twenty-four hours, with 50 to 100 mg. orally, three or four times daily, as needed. Another group of patients studied by the same author as suffering from metrorrhagia, dysmenorrhea, or menopausal symptoms treated with diethylstilbesterol with severe vomiting, were able to tolerate it as well as Progesterone and hexestrol when oral Benadryl was given simultaneously. Histadyl was of equal value.

In 1948, Budnitz[128] reported Benadryl as reducing the severity of symptoms in all of ten patients suffering from Parkinson's disease for two to fourteen years, the dose being 50 mg. four times daily, for three to fourteen months. When the drug was withdrawn and when Pyribenzamine was substituted, the return of symptoms occurred. Tolerance did not develop; larger doses did not produce added improvement, and there was no increase in the benefits over those observed at first when treatment was prolonged. A synergistic action with parasympathetic-inhibitory drugs and Benadryl was observed in four patients who used them simultaneously. Confirmation of this work by Pettit,[129] by Spickler[130] and by Gates[131] were soon forthcoming, with a complete report by Ryan and Wood,[132] who have treated forty patients since 1947. The therapeutic effect was noted to reach its maximum in ten days. The belladonna, if used, must be withdrawn gradually. Complete relapse occurs within forty-eight hours after cessation of Benadryl treatment; two patients in this series had taken 200 mg. daily for over eighteen months with no ill effects.

That Benadryl may be useful in contact dermatitis due to atropine is seen in the report by Fralick and Kiess,[133] who had nine patients with atropine dermatitis, the patients also being sensitive to hormatropine, scopolamine and duboisine. The local use of Benadryl and the oral administration of Pyribenzamine made it possible to continue the treatment of the iridocyclitis with no ill effects.

For the control of allergy to antirabic vaccine, Slipyan[134] administered 50 mg. of Benadryl to relieve the generalized urticaria which developed in a ten-year-old boy who, during prophylactic therapy, was also given 300,000 units of penicillin intramuscularly for two successive days. The allergic reactions re-appeared when the Benadryl was withdrawn but responded to subsequent re-administration. Patch tests

to penicillin and rabies vaccine were positive only for the vaccine. Pickar and Kramer[135] used Benadryl in a twenty-six-year-old patient, who developed encephalomyelitis with confusion, disorientation, and circulatory collapse, without paralysis after ten injections of phenol-killed anti-rabies vaccine. A prompt improvement in all symptoms followed the administration of 100 mg. Benadryl intravenously in 1,000 c.c. of 5 per cent glucose saline, in addition to 100 mg. orally four hours later. The drug was continued for nine days when extreme somnolence necessitated its discontinuance. The temperature rose and the symptoms recurred, this time being completely counteracted by 100 mg. doses of Pyribenzamine given three times daily for seven days.

The ends to which physicians will go in attempting to discover conditions for which antihistaminic agents are specific is shown in the work of Wilson[136] who reports on thirty-eight patients with granular proctitis who had responded to no other therapy. Given 50 mg. of Benadryl three times daily for two to eighteen weeks, benefit was seen in twenty patients with considerable improvement in fifteen more. The author feels that the relief was greater than those attributable to the sedative and antispasmodic effects of the drug, although no antihistaminic action could be demonstrated. In some patients, the nausea present may increase until the patient becomes accustomed to the drug. Benadryl has also been used in infantile gastroenteritis by Neumann[137] who found that starvation resulted in a reduction of the average number of stools from ten to three and one-half a day, although four of twenty-four infants died. Sixteen babies in the second group received the same treatment; that is, starvation and saline or Hartmann's solution orally or parenterally, with buttermilk and Benadryl in doses of 1 mg. for every month of age every four hours until improvement occurred and then four times daily. The number of stools decreased from eleven to four, although the fever was uninfluenced. The condition of the babies deteriorated when Benadryl was discontinued.

A medical research unit of the U. S. Navy[138] attempted to measure the efficacy of Benadryl in the therapy of rheumatic fever. No clinical significant improvement nor decrease in the frequency of arthralgia or the incidence of coryza occurred in eight patients given 50 mg. orally every four hours up to 300 mg. daily for the first five days and then 400 mg. daily for the next seven days, and finally 900 mg. daily for nine days. In five patients, mild drowsiness was observed, and blurred vision and dryness of the mouth occurred respectively in seven and five more. The patients demonstrated withdrawal symptoms such as anorexia, nausea, headache, vomiting and facial erythema when treatment was discontinued. Serial histamine flare tests were made on all patients before and at regular intervals during Benadryl therapy to insure effective dosage levels.

It would appear that Benadryl is efficacious in the treatment of polyarteritis nodosa. According to Sutherland,[139] a patient with a typical clinical picture of this condition given Benadryl alone was not helped. When, in addition, histamine azoprotein was injected, there was no exacerbation from the disease and the patient was able to return to work, his weight remaining stationary and the B.S.R. normal.

In 1945, Williams[140] reported relief from the syndrome of physical allergy of the head, perennial vasomotor rhinitis, myalgia, Ménière's disease and vasodilating pain, as evidenced thirty minutes after the ingestion of Benadryl (50 mg.), the effect lasting about two hours. The average patient could be maintained relatively asymptomatic with Benadryl (300 mg.), given in six divided doses at two-hour intervals. Ten of twelve patients with vasomotor rhinitis were almost completely relieved. Four patients with hyperplastic ethmoiditis obtained marked relief with retraction and disappearance of polypoid tissue and diminution or disappearance of the purulent discharge. The symptoms tended to return within twelve hours after cessation of treatment. Five patients with myalgia reported 40 to 50 per cent relief, and two patients with Ménière's disease obtained 75 to 80 per cent relief. Two patients,

who refused further treatment, complained of severe vertigo appearing within forty-five minutes. Four patients experienced difficulty in accommodation and many patients complained of drowsiness and extreme nervousness.

In 1947, Goodman and Coonrad[141] described the prophylactic effect of Benadryl in experimental histamine headache. In twenty-two of thirty-four individuals subject to headaches of various types, the injection of histamine phosphate (0.3 mg.) induced headaches which could be prevented by Benadryl (100 mg.) given orally one hour before a second histamine injection, the results being 100 per cent effective. In another fifty-four patients, in thirty-one of whom histamine reproduced their headaches, of the eighteen given Benadryl, fifteen responded satisfactorily. The author reported that Benadryl was 92.5 per cent effective in forty patients who had previously developed head pains following histamine injections. Four control cases given a placebo developed headaches on repetition of the histamine injection. Lee,[142] however, reported that Benadryl was unsuccessful in the treatment of histamine headache. Rainey[143] also in reporting on 121 patients with aural vertigo treated with unspecified intravenous doses of histamine phosphate, noted that Benadryl and/or Pyribenzamine had been given to some patients without effect, and in some cases intensified untoward reactions, although 83 per cent showed excellent results following the intravenous injection of histamine phosphate alone, with 25 per cent of the patients requiring additional courses of treatment.

Benadryl has been used in the treatment of solar urticaria. Beal[144] reported not only that the serum of two patients could be passively transferred to the skin of normal individuals who responded to the ultra-violet radiation, but also that both patients responded to two daily doses of Benadryl, 100 mg. and while thus protected were desensitized by increasing exposures to ultra-violet radiation. Sensitivity to cold has been treated by Notier and Roth,[145] the patients showing a 50 per cent improvement after Benadryl, 50 mg., had been taken four times daily for eighteen days. Gastric distress made it necessary to reduce the dose to 100 mg. daily. Symptoms returned within two weeks after cessation of treatment. Mullinger and Bogoch[145] reviewed the literature and added a case report of a patient hypersensitive to cold, who improved only slightly after taking Benadryl, 100 mg., twice daily for twenty-four days. The untoward reactions included drowsiness, nervousness, polydipsia and polyuria. Similar results were obtained with Pyribenzamine in 50 mg. doses four times daily for five days. In this patient, desensitization with subcutaneous histamine injections was without success.

Wide publicity has been given to the paper by Brewster,[147] who stated that the early administration of Benadryl, 50 mg. in adults and 10 to 25 mg. in children, at the onset of a cold completely aborted those of virus origin in 10 per cent of 100 patients, shortening the cold and giving marked relief to 95 per cent. The serous discharge from the mucous membrane of the upper respiratory tract is reported as being inhibited and subsequently also the cough reflex since postnasal drip was eliminated. The drug is said to abort the common fever blister when taken at the initial appearance of the wheal, and although there is no antipyretic effect, the soporific properties produce refreshing sleep. In a later paper, Brewster[148] used not only Benadryl but also Histadyl, and Thenylene (methapyriline), Neo-Antergan and Pyribenzamine with which 572 patients were treated. In nineteen of twenty-one, all symptoms were aborted within the first hour after the onset of symptoms, and in forty-eight of fifty-five patients, within two hours. Of 156 patients who received treatment within six hours, 116, and of 234 patients who received treatment within twelve hours, 165, were also "cured." The parallel controls treated with codeine and papaverine showed less favorable results. From the author's personal experience, seven antihistaminic preparations taken at intervals of three hours for a common cold, typical in all manifestations, were completely without effect. On the other hand, Gordon[149] used not only Benadryl but also Pyribenzamine and Thephorin, reporting

88 per cent of the patients relieved by 50 mg. doses every four to six hours, occasionally producing insomnia. A careful study of all of the papers on this subject shows that none are convincing, especially in the cases in which the antihistaminic agent was used with other substances known to give symptomatic relief. Time alone can prove the value of these drugs in virus or bacterial respiratory tract infections.

Benadryl, 150 to 200 mg./day, has been used in the lepromatous leprous reaction by Mom,[150] four of six patients obtaining relief in five to eight hours after the start of an eight to ten days course. In two patients the drug was stopped after six days, there being no relapse in thirty to seventy days. Box[151] confirmed this work in three patients treated with 50 mg. doses three times daily and for four additional patients, whose acute reactions were apparently precipitated by promin. In all cases, the courses of reaction seem to have been shortened and no new ulcers developed. The patients required no sedatives. In one patient the lesions improved and grew worse as Benadryl was repeatedly administered and withdrawn.

Of major interest is the paper by Stephens and Holbrook,[152] who in 1949 reported on eleven patients with collagen disease, four of whom were treated with Benadryl, 300 to 600 mg./daily. The seven untreated and one treated patient died within one to thirteen years after the onset of the disease. Autopsies confirmed the diagnosis. Three treated patients soon became asymptomatic. One who has continued treatment has remained free of symptoms for a year.

In 1945, Curtis and Owens[153] reported eleven of eighteen patients with acute or chronic urticaria who promptly relieved by oral Benadryl. Three patients were improved and four were not benefited. The effective dose was 50 mg. three times daily, with symptoms recurring when treatment ceased. Two patients complained of drowsiness and muscular soreness and one patient presented such severe vertigo, weakness and dizziness that the drug was discontinued. Two patients who took the drug for six months showed no toxic symptoms. At the same time, Shaffer et al[154] reported on eight patients, of whom seven received immediate relief from their chronic urticaria with 50 mg. of Benadryl four times daily. Relief occurred in thirty minutes for a patient with pruritus, in two days for a case of lichen urticatus and in two weeks for a patient with atopic eczema of thirty years' duration. In one patient with neurodermatitis, who was relieved by 50 mg. four times daily, the symptoms recurred when the drug was discontinued and thereafter the drug was ineffective in this patient, as it was in three others with neurodermatitis, dyshidrotic eczema and chronic lichen urticatus.

A report by O'Leary and Farber[155] showed that thirty-four of fifty patients with urticaria were completely relieved and twelve more were definitely improved on Benadryl, the pruritus disappearing in twenty to sixty minutes and the lesions in two to six hours. The duration of remission of twenty-five patients entirely relieved of chronic urticaria varied from one to three months. Those patients who showed intolerance were receiving 100 mg. three to four times daily. Toxic reactions described in order of decreasing frequency were drowsiness, dizziness, dilated pupils and dry mouth. In three patients the drug was discontinued because of severe dizziness, sensations of syncope and somnolence. A confirmatory report by Todd[156] showed forty-seven of fifty-two patients with acute or chronic urticaria, completely relieved, with partial relief in four, and one relieved of the wheals, but not the pruritus. Side reactions occurred in fewer than 25 per cent of the patients, who were treated both by the oral, intravenous and intramuscular routes.

Rosenberg and Blumenthal[157] used Benadryl intravenously and improved nineteen of twenty-one patients with urticaria with 30 mg. doses in 75 to 100 c.c. of saline, the injection taking seven to twelve minutes. The relief was noted as starting on the trunk and back and ending on the extremities, with the wheals blanching immediately and disappearing within one hour, the relief lasting from three to eight hours, with subsequent improvement by oral Benadryl. In three patients there were

no recurrences. In two patients, whose urticaria followed the use of penicillin in oil and wax, the treatment was a complete failure. In three asthmatic patients, who had been unrelieved by various treatments, one was improved with intravenous Benadryl. Five patients suffering from jaundice with pruritus, gonorrheal arthritis, tabetic crises, unilateral headache and dysmenorrhea were not relieved. Eight patients demonstrated toxic reactions. In a second report, O'Leary and Farber[158] were able to describe the effects of Benadryl in 186 patients with various skin conditions. In acute urticaria, twenty of twenty-five were completely relieved after one to two days, with doses of 50 to 100 mg. daily orally every three to four hours. In chronic urticaria, forty-eight of seventy-five patients were relieved while taking the drug. Ten showed no benefit. Toxic reactions occurred in 31.3 per cent of the patients, in ten of whom the treatment had to be discontinued. In atopic dermatitis, eight of twenty-five patients were relieved of their pruritus, although in pruritus of other origin, the drug was ineffective. Of nine patients with scleroderma, seven were able to bend the fingers and make a fist two weeks after the treatment with 200 to 800 mg. per day. In only two was the benefit sustained.

That Benadryl ointment might be effective was shown by Philip,[159] who reported that in 84.4 per cent of the patients with neurodermatitis and 86.7 per cent of the patients with contact dermatitis, cure occurred with the use of an ointment containing 2 per cent Benadryl. Of the twenty-four different skin conditions, the average relief was 51.8 per cent described as complete and lasting, 21 per cent partial and 27 per cent little or no relief. No contraindications were noted. In this group, one patient with chilblains was relieved immediately upon application of the cream and had relief of symptoms throughout the cold months, although treatment was discontinued. The same cream, however, was used by Perry[160] in twenty-two patients suffering from various pruritic dermatoses, no significant relief being observed. The ointment was shown as not being absorbed sufficiently to decrease the diameter of the erythema in the size of the experimental histamine wheal in five patients following local application. In six of the patients whose itching was moderately relieved, in four equal relief was obtained by the application of the ointment alone. The contradictory nature of the reports on topical application with Benadryl is shown by the work of Orecklin.[161] He used the 2 per cent ointment on 102 patients with generalized or local neurodermatitis. Seventy-seven were relieved; thirty-six of fifty-one patients with contact dermatitis and thirty-one of forty with nummular eczema, as well as twenty-eight of thirty-seven with pruritus ani vulvae or scroti, while twenty-four of thirty-eight with miscellaneous dermatoses were improved. In some instances, the ointment had to be applied every two to three hours, and even though relief of the pruritus occurred, many patients had exacerbations, some in either the same or in new locations four to six months after treatment. In this series, two per cent of the patients showed signs of sensitization or irritation following topical application. A single case of summer prurigo is reported by Woolhandler[162] as being successfully treated by Benadryl.

It is obvious that Benadryl would be used in serum sickness and Peterson and Bishop[163] at a very early date described its success in both the early and late symptoms in ten children, aged two months to ten years, who suffered from meningitis, tetanus or diphtheria. A single dose of 50 to 100 mg. lasted six to twelve hours. The symptoms of serum sickness were completely abolished in two to three hours. The side reactions occurred more frequently when the drug was given as an elixir than as a powder. The authors feel that since the drug is probably effective in proportion to its concentration in the tissues, infants require two to three times as much per pound of body weight as do adults.

In 1946, Blank[164] described his experience with the intramuscular administration of Benadryl, 5 mg., relieving three patients with urticaria whose symptoms were subsequently controlled with oral doses of 50 mg. In one patient lethargy always fol-

lowed the use of the drug. In addition, oral administration, 10 mg., relieved a child with edematous food allergy. One patient with angioneurotic edema suffered a headache, nausea, and lethargy after administration of Benadryl deriving no benefit from the drug. Therapy also failed in a patient with cold allergy. Patients with asthma did not respond. In Lockey's series[165] of 171 patients, those with hay fever, acute and chronic urticaria and perennial vasomotor rhinitis, responded, but those with intractable asthma, migraine, atopic dermatitis, erythema nodosum, sea or motion sickness and dysmenorrhea showed no response. Lockey stated that side effects were frequent and severe. Two patients with asthma, receiving 300 to 400 mg. daily for five days, developed hallucinations and extreme drowsiness. One of these died suddenly. Friendlaender[166] had previously noted no definite therapeutic effect as seen in nineteen cases of bronchial asthma. An equal number of hay fever patients, who received 50 mg. three times daily, showed only two as claiming relief and two temporary improvement. The results, however, were coincident with a decreased pollen count. In sixteen of forty-seven patients there was drowsiness, dizziness, faintness and gastrointestinal upsets. Three patients were completely intolerant to the Benadryl, although in two acute and eleven chronic cases of urticaria definite improvement, lasting two to twelve hours was seen within one hour after administration of 50 mg. In these same patients, trial diets were given to those sensitive to foods, during temporary discontinuance of the drug. Such symptoms as were reproduced by an aggravating food were controlled by the drug.

Blumenthal and Rosenberg[167] used Benadryl to treat a number of unrelated conditions. Their report claims relief in twenty-four of twenty-nine patients with urticaria; fifteen of twenty-three with seasonal hay fever; one of twelve with bronchial asthma; twelve of sixteen with contact dermatitis; five of ten with functional dysmenorrhea; four of eleven with migraine; one of three with vasomotor coryza; two with spastic colon; and two with cough and mild asthmatic wheeze were also markedly relieved. Intravenous administration of Benadryl (20-50 mg./75-100 c.c. isotonic saline) solution controlled the pruritus of ten of eleven patients with urticaria and two with contact dermatitis, although two patients with bronchial asthma and one with tabetic crisis were not helped. Oral administration of Benadryl is believed useful in preventing severe transfusion reactions. The majority of the small group of patients with pruritus due to sunburn, jaundice and psoriasis were also reported as benefited. The inconsistency is shown by the report of Engelsher[168] who found aggravation or no relief to occur in 127 of 193 patients, of whom only nine were definitely improved and the others, mildly so, although given either Benadryl or Pyribenzamine in more than adequate dosage.

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(To be continued in the May-June issue.)

COMPARATIVE STUDIES OF CERTAIN ANTIHISTAMINE DRUGS

(Continued from Page 233)

in many pharmacological respects. It is reasonable to assume that these drugs will give different results clinically. In some circles, there is an evident tendency to group all of the antihistamine drugs together. This is unwarranted.

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WHAT IS TO BE OUR BASIC PROFESSIONAL RELATIONSHIP?

(Continued from Page 239)

begins with symptoms and goes on to attitudes which have been denied to awareness, the perception of the relationship between these denied attitudes and her behavior, the reorganization of self to include these denied attitudes, and the consequent alteration of behavior.

CONCLUSION

I have tried to indicate the possibility that a very different relationship is called for in dealing with physiological and psychological problems. In handling organic problems, the relationship is most effective if responsibility, learning, and accurate, objective evaluation are lodged primarily in the expert. In dealing with psychological conflict, our work would indicate that the responsibility, the self-initiated learning, and accurate perception and evaluation of inner experience must be lodged with the client. The expert has an effective relationship with the individual when he is able to create the atmosphere which facilitates such processes in the client.

The worker in psychosomatic medicine is at the heart of the problem created by the need for these two different types of relationships. How can he deal effectively with both elements—those organic aspects over which the patient can have no conscious control, and those psychological elements which can potentially come into awareness and thus under conscious control? I cannot give you the answer, but I think the first step in finding the answer is to face the basic contradiction in relationships which I have tried to pose.

University of Chicago

News Items

SOUTHWEST ALLERGY FORUM

A very well attended and enthusiastic meeting marked with the usual Southern cordial hospitality was held at the Hotel Peabody in Memphis April 2-4. There were five round tables covering important subjects in allergy. President John H. Mitchell of the American College of Allergists and President Theodore F. Squier of the American Academy of Allergists gave luncheon addresses. Social activities featured a cocktail party followed by a banquet the first evening of the session.

NEW ARGENTINE ORGANIZATION

A new allergy organization has been formed in Argentina known as the Associatión de Alergia e Inmunologia. The address is Cangallo 1435, Bueños Aires. The executive committee is as follows: President, Dr. Benigno R. Garat; Vice-president, Dr. José A. Bózzola; Secretary, Dr. Carlos R. Landa; Treasurer, Dr. Osvaldo Rossi Richeri; Chief Editor, Dr. Rubén A. Binaghi. This is not to be confused with the older allergy society in Argentina known as Sociedad Argentina de Alergia, which is an official member of the International Association of Allergists.

It is earnestly hoped that there will be cordial relations between the two national societies, which is so essential for the best interests of allergy not only in the Argentine but in promoting international relationship with allergy societies of other countries.

PSYCHOTHERAPY COURSE FOR ALLERGISTS

Your attention is called again to the Psychotherapy Course for Allergists to be given by Dr. Sandor Rado, Clinical Professor of Psychiatry and Director of the Psychoanalytic Clinic for Training and Research, Columbia University, beginning Monday, November 6, and ending Friday, November 10, 1950. The course is being given with the co-operation of the American College of Allergists. Other members of the staff of the Psychoanalytic Clinic will also participate in the program of the course. Lectures will be held from 9:00 a.m. to 12:30 p.m. and from 2:00 p.m. to 5:00 p.m. daily, and it may be that evening round-table discussions will be presented also.

The registration is limited, but there are some vacancies left. The registration fee is $100. Write to Dr. Harold A. Abramson, 133 East 58th Street, New York, New York, for details. This is a privileged opportunity for you to increase your understanding of the relation of psychodynamics with basic medical sciences. You will have the advantage over other allergists who do not appreciate the importance of psychosomatic allergy at the present time. The course will also familiarize you with the psychological aspects of the patient-physician relations and with the techniques of the minor psychotherapy of the allergic patient.

HUNGARIAN SECTION OF ALLERGISTS

The section of Hungarian allergists held its symposium entitled "Liver and Allergy," on October 20, 1949, at Budapest. Pathologists particularly interested in liver diseases participated in the proceedings. Following the chairman's introduction, Doctor Farkas presented the histological changes, interpreted as allergic, in asthma, eclampsia, and endophlebitis. Doctor Farkas agreed that allergic factors play an important role besides the icterogenic virus in the etiology of infective hepatitis. The discussants were Drs. Filipp, Vegh, Kobulniczky, Rajka, Fornet and Hajos.

Drs. M. K. Hajos, O. Riedl and G. Szecsey spoke on the hepatic reactions in allergic diseases, indicating that 30 per cent of allergic patients, mainly those with asthma, showed abnormal liver function tests. They emphasized the importance of introducing more exact methods for investigation of liver functions. In the discussion, Doctor Radnoti proposed the determination of differential-nitrogen as an important diagnostic test. Doctors Filipp, Kelenhegyi and Jona discussed in their lecture the organic liver shock, and found that hepatic lesions resemble the Masugi kidney. Animal experiments revealed abnormal liver function tests along with histopathological changes. On the day following, the section on allergy held its regular session.

Dr. L. Mosonyi described allergic investigations in the Soviet Union. Doctors Kemeny and Filipp discussed "Hypophysis and Anaphylaxy," and stated that hypophysectomy rendered animals susceptible to anaphylaxis, and that anterior pituitary lobe extracts inhibited the shock. Doctor Hajos mentioned his own experiments concerning the relation of endocrine function and anaphylaxis.

Doctor Hajos gave an address on "Environmental Influence in the Etiology of Allergic Diseases" and enumerated exogenous factors and social problems influencing allergic diseases. Following this there was a discussion by Doctors Filipp, Csefko, Vegh, Kerdo, Fornet and Rajka. Dr. E. Feher discussed micogenic allergy. Doctor Mosonyi presented "Antibiotics and Allergy." Doctor Rudas remarked on the successful desensitization to penicillin and streptomycin.

PENNSYLVANIA ALLERGY ASSOCIATION

The program of the Pennsylvania Allergy Association which will meet at the Bedford Springs Hotel on May 11, 1950, is as follows:

Wednesday, May 10, 1950

9:00 P.M. Parlor "A"—Board of Regents Meeting

Thursday, May 11, 1950

9:00 A.M. Parlor "A"—Business Meeting for Members
12:30 P.M. Parlor "A"—Luncheon for Members and Guests
7:30 P.M. Parlor "A"—Banquet for Members and Guests
Chairman of Scientific Session—Morning, H. A. SLESINGER, M.D., Windber. Afternoon, BEN HAMNER, M.D., Williamsport.

Scientific Exhibits

Anthrocilicosis and Pediatric Allergy—H. A. SLESINGER, M.D., Windber
Inhalation Therapy and Botanical Slides—STEPHEN LOCKEY, M.D., Lancaster
The Problem of Bronchial Asthma—WILFRED LANGLEY, M.D., Sayre
Pictures of Molds—JOSEPH PIEKARSKI, M.D., Wilkes-Barre

Morning Session

9:50 A.M. "Welcome"—President of Bedford Medical Society
9:55 A.M. "Welcome"—L. R. ALTEMUS, M.D., 11th District Councilor
10:00 A.M. "Explosive Reaction in Dermatologic Allergy"—JOSEPH RICCHUITI, M.D., Pottsville
Discussion opened by WILFRED LANGLEY, M.D., Sayre
10:30 A.M. "The Botany of Allergy"—EDWARD CLAUS, M.D., University of Pittsburgh, Pittsburgh
Discussion opened by RUTH WILSON, M.D., Beaver
11:30 A.M. "Gastro-intestinal Manifestations of Allergy During Childbirth"—JOSEPH FRIES, M.D., Brooklyn, New York
Discussion opened by LUTHER KING, M.D., Meadville.

12:00 P.M. "X-Ray and Its Importance in the Diagnosis and Treatment of Allergic Disorders"—WALTER WERLEY, M.D., Reading
Discussion opened by NICHOLAS SARGENT, M.D., Falls Creek
12:30 P.M. Intermission

Afternoon Session

2:00 P.M. "Drugs in Allergic Therapy"—STEPHEN LOCKEY, M.D., Lancaster
Discussion opened by JAMES MANSMANN, M.D., Pittsburgh
3:00 to 5:00 P.M.—"The Present Status of Bacterial Allergy"

"Ask the Experts"

A question and answer quiz with a minimum of prepared statements.
Please participate by presenting your problems

Panel Members

RICHARD A. KERN, M.D.—Professor of Medicine, Temple University, Philadelphia
"The Present Status of Bacterial Allergy" (10 minutes)

RUSSELL C. GROVE, M.D.—Chief Otologist, Allergy Clinic Roosevelt Hospital, New York City
"Bacterial Allergy in Otorhinolaryngology" (10 minutes)

JOHN E. GREGORY, M.D.—Head, Division of Pathology, Hahnemann Medical College, Philadelphia
"The Role of Allergy in Rheumatic Fever" (10 minutes)

ARCHIBALD R. JUDD, M.D.—Superintendent, Pennsylvania State Sanatorium of Tuberculosis No. 3, Hamburg, Pennsylvania (10 minutes)

Moderator

PAUL C. CRAIG, M.D.—Secretary for Instruction, Pennsylvania Academy of Ophthalmology and Otolaryngology

RALPH M. MULLIGAN, M.D.
Secretary-Treasurer

CORRECTION

In the paper entitled "Cottonseed Protein vs. Cottonseed Oil Sensitivity" published in the January-February number of the ANNALS, the following corrections should be noted:

The third footnote on Page 4, Table II, should read "Ratio of specified threshold to ingestion threshold."

On Page 5, Paragraph 5, line 6 should read: "was relatively great, from one-sixth to one-three hundredth the ingestion doses being required to ex-."

HYPO-ALLERGIC PENICILLIN

(Continued from Page 201)

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BOOK REVIEWS

MEDICAL ETYMOLOGY. The History and Derivation of Medical Terms for Students of Medicine, Dentistry, and Nursing. By O. H. Perry Pepper, M.D., Professor of Medicine, University of Pennsylvania. 263 pages. Price $5.50. Philadelphia: W. B. Saunders Company, 1949.

This handbook is the answer to a rapidly new and bewildering medical, dental, and nursing terminology. Medical schools in general do not have an adequate course in scientific terminology. The book gets away from the style of a dictionary, since it is concerned more with the origin or derivation of words than with the meaning. Its less than 4,000 terms represent almost all of the roots the student will encounter, so that he will be released from slavish dependence on a medical dictionary with its 50,000 or so words. The data in the book are presented in a manner to be available and helpful to the student.

There are four parts, the first of which consists of an introduction giving background of medical terminology, prefixes, suffixes, compounds and transliteration, eponyms, and onomatopoietic words.

The second part deals with preclinical subjects, the third with clinical subjects, and the fourth with dentistry. There is a comprehensive index which serves also as a ready reference for the spelling or the difficult medical terminology commonly used. All authors could use this book to great advantage in improving their writing.

PSYCHIATRY IN GENERAL PRACTICE. By Melvin W. Thorner, M.D., D.Sc., Assistant Professor of Neurology, The Graduate School of Medicine, University of Pennsylvania, with a foreword by C. Charles Burlingame. 659 pages. $8.00. Philadelphia: W. B. Saunders Company, 1949.

The author's purpose is aptly expressed when he states, "This volume is an attempt to lift psychiatry out of the realm of *terra incognita* for those whose primary efforts are spent in other fields."

The book is characterized by presenting psychological medicine that is very interesting from the professional point of view, yet avoiding the sensational. Such a book obviously must present case histories which represent actual experience with patients. The author succeeds admirably in doing this. The book is a departure from the many texts on the subject which do not recognize the importance of the association between psychiatrists and men in other branches of medicine. For the internists and general practitioners who wish to apply psychiatry in their practice, it is most valuable. It is written in understandable language for those who see and treat *patients* rather than for the academic psychiatrist or the psychoanalyst. The patients' problems are presented first, followed by logical generalizations and deductions.

The volume is well organized, and the material is arranged roughly in three sections. Each section has a list of excellent selected references. There is an appendix of classification of mental disorders, as well as one of committal procedures.

The book is well bound, the print is very clear and readable, and the case reports are in italics.

1950 CURRENT THERAPY. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D., with Twelve Consulting Editors and 269 Contributors. 736 pages and numerous tables. Price $10.00. Philadelphia and London: W. B. Saunders Company, 1950.

This is the second annual volume of a book which is different both in concept and in content from any other book of its kind. There are sixty-three pages of additional material this year, and it affords a ready desk reference of detailed, authoritative articles on the very latest treatments for every disease and condition encountered by

the practicing physician or the specialist, whether the disease occurs frequently or rarely. Every effort is made to present the best treatment available today for that particular disease, according to the Board of Consultants, who selected each contributor as an authority with practically the most effective treatment for any disease in question. Experimental or highly controversial methods are omitted, and the volume does not represent excerpts from the literature but the actual experience of the contributors.

Each article was written especially for this text and represents the work and report of a foremost authority describing the method he is using in treating this particular disease at the present time.

The section on allergy comprises pages 407-441, including all of the diseases definitely known to be due to allergy.

The book is very durably and attractively bound, and the two-column style facilitates reading. It is arranged in fourteen convenient sections. Each section is prefaced by a "Contents" page listing alphabetically where each disease may be found in the book. The text has had a phenomenal distribution since its appearance last year, and any practicing physician or specialist in any field of medicine will find readily at hand a concise, authoritative treatment of diseases in general.

A STUDY OF THE ANTIGENICITY OF ATOPIC REAGIN

(Continued from Page 222)

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